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(54) **ANTIBACTERIENS A BASE DE PYRONINE, PROCEDE CORRESPONDANT ET INTERMEDIAIRES NOUVEAUX**

(54) **PYRONIN ANTIBACTERIALS, PROCESS AND INTERMEDIATES**

(57) L'invention concerne des procédés convergents de préparation de myxopyronines et de corallopyronines, composés qui sont utiles en tant qu'agents thérapeutiques antibactériens. L'invention se rapporte également à des compositions nouvelles d'éléments utiles à la préparation d'antibiotiques à base de pyronine.

(57) The present invention provides convergent processes for preparing myxopyronins and corallopyronins, compounds useful as antibacterial therapeutics. The present invention also provides novel compositions of matter which are useful for the preparation of pyronin antibiotics.

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(57) Abstract

The present invention provides convergent processes for preparing myxopyronins and corallopyronins, compounds useful as antibacterial therapeutics. The present invention also provides novel compositions of matter which are useful for the preparation of pyronin antibiotics.

PYRONIN ANTIBACTERIALS, PROCESS AND NOVEL INTERMEDIATES THERETO

Field of the Invention

The present invention is in the field of pyronin antibiotics. In particular, the present invention relates to processes for the preparation of myxopyronins and corallopyronins, compounds useful as antibacterial therapeutics. The present invention also provides novel compositions of matter which are useful as intermediates for preparing the pyronin antibiotics.

Throughout this application, various publications are referred to, each of which is hereby incorporated by reference in its entirety into this application to more fully describe the state of the art to which the invention pertains.

Background of the Invention

Myxopyronins and corallopyronins are 2-pyrone-containing antibiotics which present a significant opportunity in antibacterial therapy. They constitute a

synthetically accessible, unexploited series of low molecular weight bacterial RNA polymerase (RNAP) inhibitors with favorable properties: selectivity vs. human RNAP, cell penetration (minimal inhibitory concentrations (MICs) at concentrations comparable to *in vitro* bacterial RNAP IC_{50}s), and potency against rifampicin-resistant *S. aureus* equal to that against a rifampicin-susceptible strain.

Corallopyronin A/B and myxopyronin A/B are natural products isolated from gliding bacteria (*Corallococcus coralloides; Myxococcus fulvus*) and discovered to be RNAP inhibitors. Reichenbach, H., Höfle, G., Irschik, H., Kohl, W., *Liebigs Ann. Chem.*, **1983**, 1656; Reichenbach, H., Höfle, G., Irschik, H., Kohl, W., *Liebigs Ann. Chem.*, **1984**, 1088; Reichenbach, H., Höfle, G., Irschik, H., Jansen, R., *Liebigs Ann. Chem.*, **1985**, 822. The structures of these compounds are closely related having in common a 3-acyl-4-hydroxy-2-pyrone with an alkyl chain at the 6-position bearing a vinyl carbamate functionality, a feature atypical of natural products. They differ only in the substitution on the alkyl chain attached to the 3-position of the pyrone, the corallopyronins being more elaborate (Figure 1(a)). The pyronins have good intrinsic activity in antibacterial assays against both *E. coli* and *S. aureus* RNA polymerase. This activity is specific with respect to human or SP6 polymerases. MIC data (see Table I) show that these compounds, like rifampicin, are not absorbed well by *E. coli* but that they have intrinsic activity against both gram positive and gram negative bacteria.

Table I

	In Vitro IC_{50} (μM)					MIC (μg/ml)		
Compound	E.coli RNAP	S.aureus RNAP	Human RNAP	SP6 RNAP	Rev/RRE	S.aureus	E.coli MCR	E.coli BAS
Myxopyronin A/B	10	10	>200	>200	100	4	180	1.6
Corallopyronin A/B	6	10	>200	>200	100	4	>200	0.4

An attractive feature of this series of compounds is their activity against strains resistant to rifampicin. The MIC for rifampicin is ca. 10 nM against susceptible strains, but falls off against resistant strains (MIC> 10 μM). The use of rifampicin is limited by the development of bacterial resistance. Both myxo- and corallopyronins are equiactive against Rif-susceptible and Rif-resistant *S. aureus*.

Pyrones have been used in the prior art to elicit a biological effect in a few instances, but in none of these instances have they been used as an antibacterial agent. 2H-Pyran-2,6(3H)-dione derivatives are reported to be active at reasonable doses in a passive cutaneous anaphylaxis model in rats when administered by either the intravenous or oral route. Snader, K.M. et al., *J. Med. Chem.*, **1979**, *22*, 706; Chahrin, L.W., Snader, K.M., Williams, C.R., 2H-Pyran-2,6(3H)-dionederivate. German Patent 25 33 843. In a second case, simple 3-(1-oxoalkyl)-4-hydroxy-6-alkyl-2-pyrones were found to be effective *in vitro* in the inhibition of human sputum elastase. Cook, L., Ternai, B., Ghosh, P., *J. Med. Chem.*, **1987**, *30*, 1017. Lastly, a series of pyrone derivatives were found to be effective inhibitors of HIV protease in both enzymatic assays and cell culture (Figure 1(b)). Skulnick, H. I., et al., *J. Med. Chem.*,

1995, *38*, 4968. No synthetic investigations or medicinal uses of pyronin antibacterials have been reported in the literature.

The present invention provides novel intermediates useful in the synthesis of myxopyronin A and derivatives thereof. In addition, the present invention provides processes for synthesizing myxopyronin A and derivatives thereof as well as corallopyronins.

Summary of the Invention

One object of the present invention is to provide processes for the preparation of myxopyronins and corallopyronins, compounds useful as antibacterial therapeutics.

Another object of the present invention is to provide various compositions of matter useful as intermediates in the preparation of the antibiotic myxopyronin.

A further object of the present invention is to provide methods of preparing such intermediates.

Brief Description of the Drawings

Fig. 1(a) shows the structures of corallopyronin A/B and myxopyronin A/B.

Fig. 1(b) illustrates coumarin derivatives which inhibit HIV protease in enzymatic assays and cell culture. Skulnick, H. I., et al., *J. Med. Chem.*, **1995**, *38*, 4968.

Fig. 2 illustrates a retrosynthetic analysis for the preparation of myxopyronin A.

Fig. 3 illustrates the synthesis of compound **1** in accord with the present invention.

Fig. 4 illustrates alkylation of the 7-position of compound **3** for the preparation of compound **10**.

Fig. 5 illustrates the synthesis of compound **6** in accord with the present invention.

Fig. 6 illustrates the synthesis of compound **10** in accord with the present invention.

Fig. 7 illustrates an alternative synthesis of compound **10** in accord with the present invention.

Fig. 8 illustrates the synthesis of compound **18** in accord with the present invention.

Fig. 9 illustrates the attempted acylation of pyrone **10** with acyl chloride **19**.

Fig. 10 illustrates an alternative retrosynthetic analysis for the preparation of myxopyronin A.

Fig. 11 illustrates the synthesis of compound **18** in accord with the present invention.

Fig. 12 shows a retrosynthetic analysis of myxopyronin A.

Fig. 12(a) shows the preparation of allyl aldehyde **14**.

Fig. 12(b) shows the preparation of acylated pyrone **5**.

Fig. 12(c) shows the preparation of iodide **8b**.

Fig. 13(a) provides a synthetic route to acyl pyrone intermediate **15**.

Fig. 13(b) illustrates the condensation reaction of intermedites **14** and **15** and subsequent elaboration to myxopyronin A.

Fig. 14(a) shows the preparation of allyl aldehyde **14**.

Fig. 14(b) shows the acylation of pyrone **10** with propionyl chloride and subsequent elaboration to myxopyronin A.

Fig. 15 provides a synthetic route to intermediate pyrone **10**.

Detailed Description of the Invention

The present invention provides a convergent synthetic route to prepare myxopyronin compounds. The invention provides two variant pathways based on alternative

approaches to install the side chain at the pyrone 3-position.

Pathway A

Starting with 2-pentanone, a Wadsworth-Emmons reaction is performed with triethyl phosphonoacetate in THF in the presence of NaH. Ester **16** (see Figure 3) is sequentially reduced with DIBAL and oxidized with DDQ to produce aldehyde **14**. A Wadsworth-Emmons reaction is used to condense aldehyde **14** and triethyl 2-phosphonopropionate in THF in the presence of NaH. The resulting product is sequentially reduced with DIBAL and oxidized with DDQ to produce aldehyde **1**. This constitutes the 3-position side chain precursor.

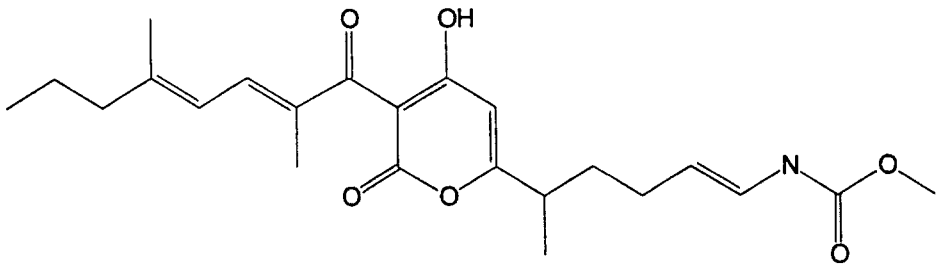
The pyrone portion is constructed as follows. Ethyl propionylacetate is hydrolyzed with aqueous NaOH. Two equivalents of the resulting acid are condensed with an equivalent of carbonyldiimidazole to produce pyrone **5** (see Figure 5). The 3-propionyl group is hydrolyzed using concentrated H_2SO_4 at elevated temperature to afford pyrone **6**, which is then alkylated with 3-bromopropionaldehyde dimethylacetal using n-BuLi and THF/HMPT as a solvent to give **7**. The 4-position hydroxyl is converted to SEM ether **8** using SEM-Cl and diisopropylamine in CH_2Cl_2. The dimethylacetal is removed under acidic conditions and the resulting aldehyde is alkylated under Wadsworth-Emmons conditions with triethylphosphonoacetate in THF in the presence of NaH to produce the unsaturated ester **9**. The SEM ether is cleaved using TBAF and DMPU to give key intermediate **10**.

Intermediate **10** can be synthesized by an alternate pathway. Pyrone **6** is deprotonated with n-BuLi and then alkylated with allyl bromide in THF/HMPT. The 4-position hydroxyl is converted to SEM ether **11** by treatment with SEM-Cl and diisopropylamine in CH_2Cl_2. The allyl group is hydroborated using a borane reagent and the subsequent borate is removed oxidatively to give the alcohol. The resulting alcohol is oxidized under standard Swern conditions to give aldehyde **12**. Aldehyde **12** was alkylated with triethylphosphonoacetate in THF in the presence of NaH to produce unsaturated ester **9**. The SEM ether is removed under acidic conditions, e.g., using H_2SO_4 in THF/EtOH, to give the key intermediate **10**. An aldol reaction between compounds **1** and **10** catalyzed by TFA in CH_2Cl_2 provides intermediate **13**. The synthesis can be finished by oxidation to produce intermediate **17** followed by a Curtius sequence to produce myxopyronin A **18**.

Pathway B

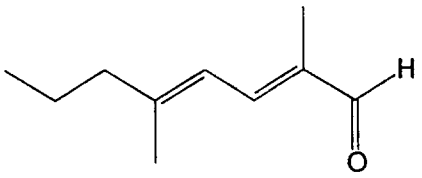
The second route takes advantage of the convenient availability of intermediates **10** and **14** by processes disclosed below. Pyrone **10** is acylated with propionyl chloride in TFA at elevated temperature to afford intermediate **15** (Figure 11). A base-catalyzed aldol between compounds **14** and **15** using LDA in THF forms an intermediate that is sequentially treated with mesyl chloride and triethylamine in CH_2Cl_2 followed by DBU to afford compound **17**, which is also an intermediate in pathway A. Myxopyronin A results after a Curtius sequence.

The present invention provides a process of preparing a myxopyronin having the structure:

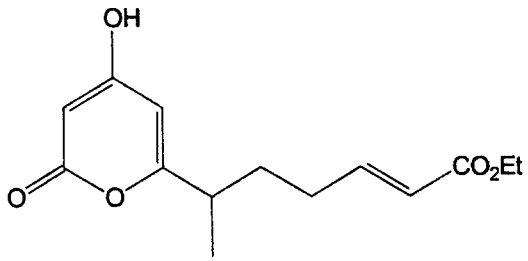


which comprises:

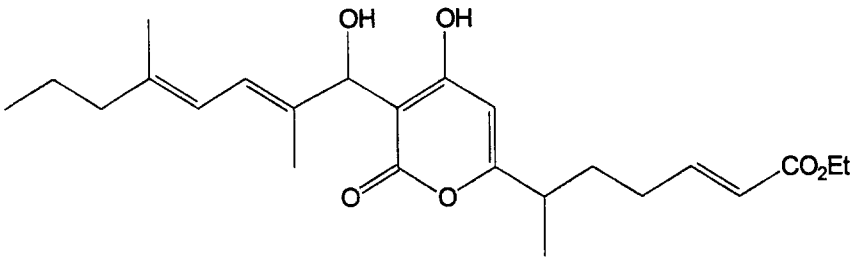
(a) condensing an aldehyde having the structure:



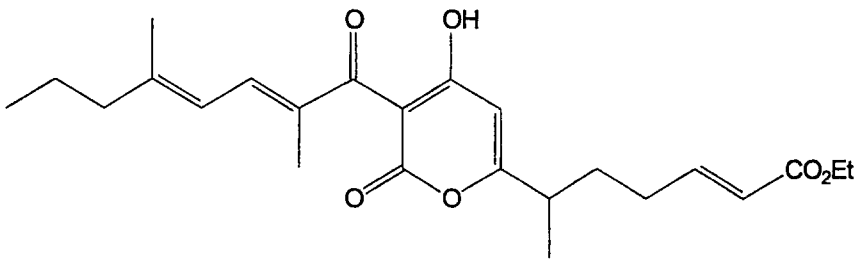
with a pyrone having the structure:



under suitable conditions to form an adduct having the structure:



(b) oxidizing the adduct formed in step (a) under suitable conditions to form a pyrone ketone having the structure:



and (c) (i) saponifying the pyrone ketone formed in step (b) under suitable conditions to form a pyrone acid;

(ii) acylating the pyrone acid formed in step (c)(i) under suitable conditions to form a pyrone anhydride; and

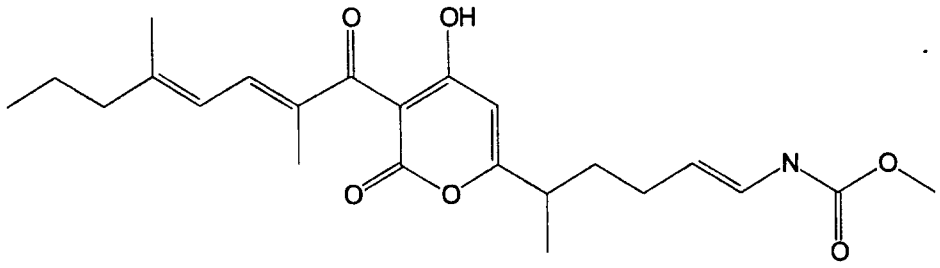
(iii) treating the pyrone anhydride formed in step (c)(ii) with an azide salt to form a pyrone acyl azide; and

(iv) heating the pyrone acyl azide formed in step (c)(iii) in methanol under suitable conditions to form myxopyronin A.

As practiced in the present invention, the 1,2-addition step (a) recited above is performed using an acid catalyst, such as trifluoroacetic acid (TFA), hydrochloric acid, sulfuric acid, or p-toluenesulfonic acid, preferably in the presence of a dehydrating agent, such as molecular sieves, more preferably using 4Å molecular sieves, in an inert organic solvent, such as dichloromethane or p-dioxane. Alcohol oxidation step (b) is carried out using various oxidants, such as 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ), manganese dioxide or chromium chlorochromate. Saponifying step (c)(i) is carried out using a hydroxide base, such as LiOH, NaOH, KOH or CsOH, in a solvent mixture comprising water and at least one organic co-solvent, such as methanol, ethanol, or tetrahydrofuran (THF). A preferred solvent composition is methanol/THF/water in the proportion 2:2:1. In the Curtius sequence, step (c)(ii) is effected

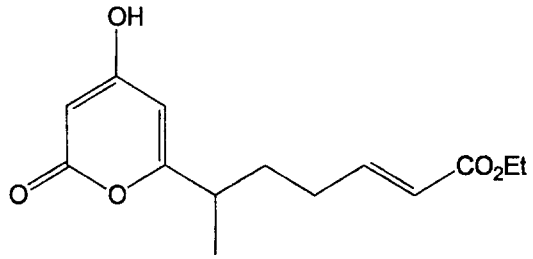
using an alkyl or aryl chloroformate, including, but not limited to, methyl chloroformate, ethyl chloroformate, isopropyl and phenyl chloroformate, in the presence of a base, such as DIPEA, in an inert organic solvent, preferably miscible with water, preferably, acetone. The resulting product may be purified, or used directly in the subsequent step. Step (c)(iii) is carried out using an azide salt, such as lithium azide, sodium azide, or tetraalkylammonium azide, preferably in the presence of water. Rearrangement step (c)(iv) entails heating the acid azide formed in step (c)(iii) in a solvent mixture, containing an alcohol, such as ethanol, methanol, or phenol, preferably, methanol, and an inert solvent such as benzene or toluene, at elevated temperatures, preferably, at the reflux temperature of the solvent mixture.

The present invention also provides a process of preparing a myxopyronin having the structure:

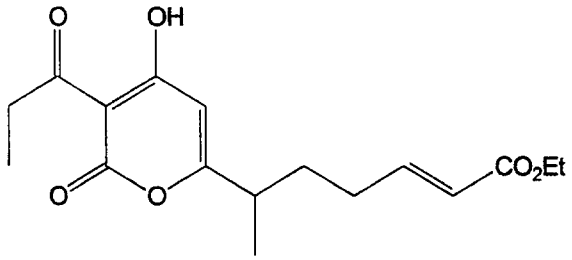


which comprises:

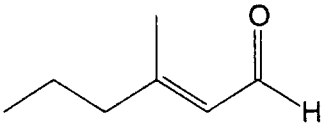
(a) treating a pyrone having the structure:



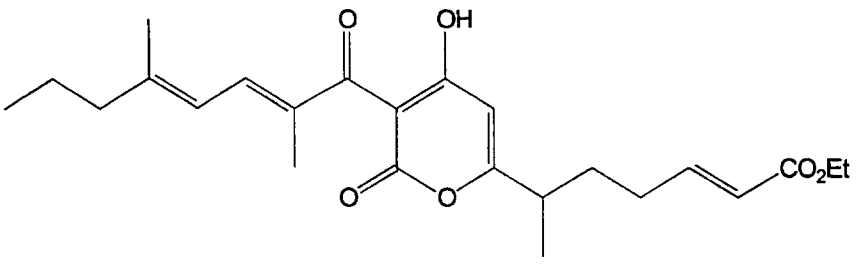
with propionyl chloride under suitable conditions to form a ketone adduct having the structure:



(b) (i) condensing the ketone adduct formed in step (a) under suitable conditions with an aldehyde having the structure:



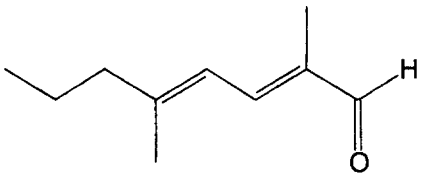
to form a pyrone aldol; (ii) mesylating the pyrone aldol formed in step (b)(i) under suitable conditions to form a pyrone aldol mesylate; and (iii) reacting the pyrone aldol mesylate under suitable basic conditions to form a pyrone ketone having the structure:



and (c) (i) saponifying the pyrone ketone formed in step (b)(iii) under suitable conditions to form a pyrone acid; (ii) acylating the pyrone acid formed in step (c)(i) under suitable conditions to form a pyrone anhydride; and (iii) treating the pyrone anhydride formed in step (c)(ii) with an azide salt to form a pyrone acyl azide, and (iv) heating the pyrone acyl azide formed in step (c)(iii) under suitable conditions to form the myxopyronin.

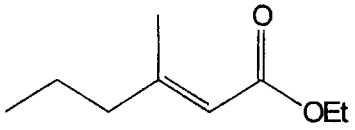
Acylation step (a) may be effected using an acid catalyst, such as TFA, hydrochloric acid, or p-toluenesulfonic acid, preferably in the presence of a dehydrating agent, such as molecular sieves, preferably using 4Å molecular sieves, in an inert organic solvent, such as dichloromethane. Condensation step (b)(i) is performed using a strong, non-nucleophilic base, such as LDA, potassium t-butoxide, or sodium hydride, preferably, LDA, in an inert organic solvent, such as THF. Mesylation step (b)(ii) is carried out using an acylating agent, such as mesyl chloride, p-tosyl chloride, acetic anhydride, preferably, mesyl chloride, in the presence of a non-nucleophilic organic base, such as DIPEA or triethylamine. Elimination step (b)(iii) may be performed using a variety of reagents effective to cause elimination, preferably, a strong non-nucleophilic base such as DBU. The Curtius rearrangment is effected as described above.

The present invention also provides a process of preparing an unsaturated aldehyde having the structure:

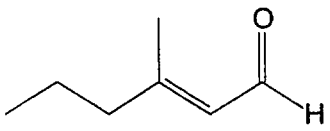


which comprises:

(a) condensing triethyl phosphonoacetate with 2-pentanone under suitable conditions to form an unsaturated ester having the structure:



(b) (i) reducing the unsaturated ester formed in step (a) under suitable conditions to form an unsaturated alcohol; and (ii) oxidizing the unsaturated alcohol under conditions suitable to form a monounsaturated aldehyde having the structure:



and (c) (i) condensing triethyl phosphonopropionate with the monounsaturated aldehyde formed in step (b)(ii) under suitable conditions to form a diene ester;

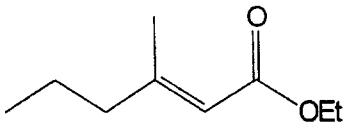
(ii) reducing the diene ester formed in step (c)(i) under suitable conditions to form a diene alcohol; and

(iii) oxidizing the unsaturated alcohol under suitable to form the unsaturated aldehyde.

As implemented in the present invention, the condensation step, preferably of the Wadsworth-Emmons type, is favorably performed in the presence of a non-nucleophilic

base, such as LDA or sodium hydride, in an inert polar, aprotic organic solvent, such as THF. The ester reduction step (b)(i) may be carried out using any of a variety of reducing agents, such as diisobutylaluminum hydride (DIBAL) in an inert aprotic organic solvent, such as THF. Oxidation step (b)(ii) may be effected using any of a range of mild oxidants, preferably, DDQ, in an inert organic solvent, such as dichloromethane. The subsequent condensation step (c)(i) may be performed in the presence of a non-nucleophilic base, such as sodium hydride, in an inert organic solvent, preferably, THF. Reduction step (c)(ii) may be carried out using various reducing agents, preferably, diisobutyl-aluminum hydride (DIBAL) in an aprotic organic solvent, such as THF. Finally, oxidation step (c)(iii) may be effected using a variety of oxidants, such as DDQ, in dichloro-methane.

In one embodiment, the present invention provides a process of preparing the unsaturated ester having the structure:

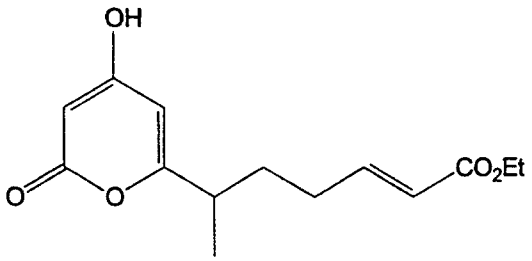


which comprises (a) condensing ethyl butyryl acetate with diethyl phosphorochloridate under suitable conditions to form an enol phosphonate; and (b) alkylating the enol phosphonate formed in step (a) with an organometallic reagent under suitable conditions to form the unsaturated ester.

As practiced in the invention, condensing step (a) is

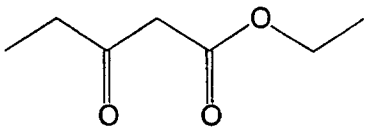
performed using a non-nucleophilic base, including, but not limited to, potassium t-butoxide, sodium hydride, LDA, and lithium diethylamide, preferably, sodium hydride, in an inert aprotic organic solvent, such as THF or diethyl ether. Alkylation step (b) is effected using an organometallic reagent, such as lithium dimethyl cuprate, methyl lithium, methyl magnesium bromide or chloride, preferably, lithium dimethyl cuprate, in an inert aprotic solvent, preferably, diethyl ether, at a temperature ranging from about -100°C to about 0°C, more preferably, from about -90°C to about -50°C, most preferably, at -78°C.

In addition, the present invention provides a process of preparing a pyrone ester having the structure:

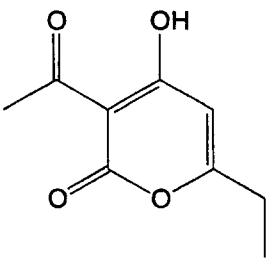


which comprises:

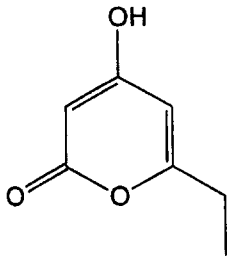
(a) treating a dicarbonyl compound having the structure:



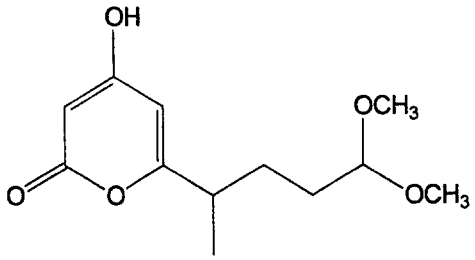
acidifying and dimerizing under suitable conditions to form an acyl pyrone having the structure:



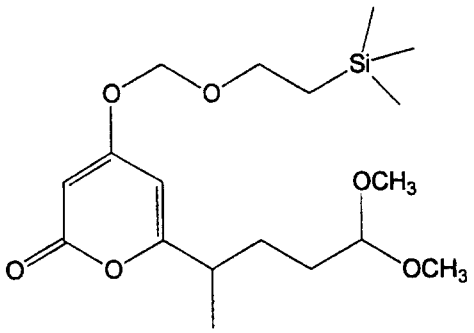
(b) hydrolyzing the acyl pyrone formed in step (a) under suitable conditions to form a pyrone having the structure:



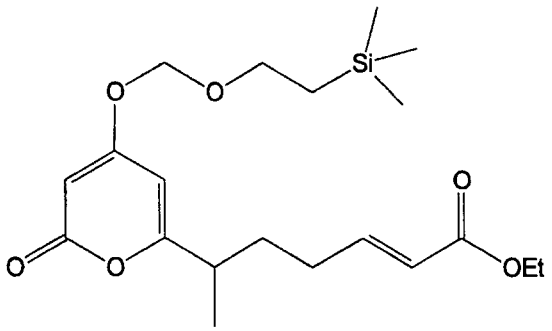
(c) alkylating the pyrone formed in step (b) under suitable conditions to form a pyrone acetal having the structure:



(d) etherifying the pyrone acetal formed in step (c) under suitable conditions to form an ether pyrone acetal having the structure:



(e) (i) acidolytically cleaving the pyrone acetal under suitable conditions; and (ii) reacting with triethyl phosphonoacetate under suitable conditions to form a protected pyrone ester having the structure:

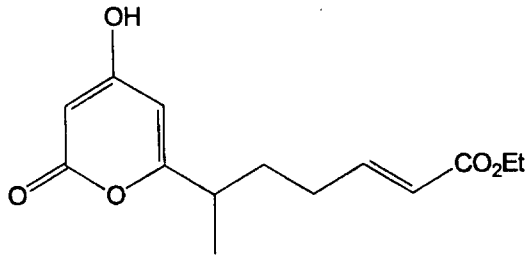


and (f) deprotecting the protected pyrone ester under suitable conditions to form the pyrone ester.

Hydrolysis in step (a) recited above is carried out using a hydroxide base, such as LiOH, NaOH, or KOH, preferably NaOH, followed by acidification with a variety of acids, including, but not limited to, hydrochloric acid, sulfuric acid, phosphoric acid, nitric acid, and TFA, preferably, hydrochloric acid. Dimerization in step (a) is effected using a condensing agent, such as carbonyl diimidazole, or an equivalent reagent known in the art. Hydrolysis step (b) is performed using a strong acid such as hydrochloric acid, hydrobromic, trifluoroacetic or sulfuric acid, preferably 90% sulfuric acid, at elevated temperature, in the range from about 65°C to about 160° C, preferably between about 100°C and about 140 ° C, more preferably, at 130°C. Alkylation step (c) with fluoro-, chloro- or bromopropionaldehyde dimethyl acetal is carried out using a strong base such as n-butyl lithium, t-butyl lithium, sec-butyl lithium or phenyl lithium, in an inert polar aprotic solvent, such as THF in the presence or absence of a co-solvent, such as HMPT. Etherification step (d) is effected using a strong non-nucleophilic base such DIPEA or triethylamine in an inert organic solvent, such as

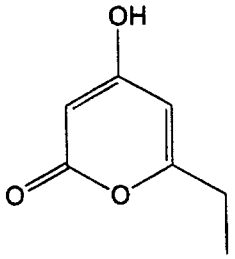
dichloromethane. Acetal cleavage step (e)(i) is carried out using a strong acid, such as sulfuric acid or p-tosic acid, in a solvent mixture preferably comprising THF and water in a ratio of 10:1. Condensation step (e)(ii) employs a strong non-nucleophilic base, such as sodium hydride, in a solvent mixture favorably comprising toluene and DMF. Deprotection step (f) utilizes an organic fluoride salt, preferably tetrabutylammonium fluoride.

The present invention further provides a process of preparing a pyrone ester having the structure:

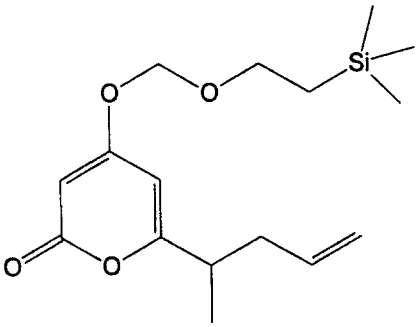


which comprises:

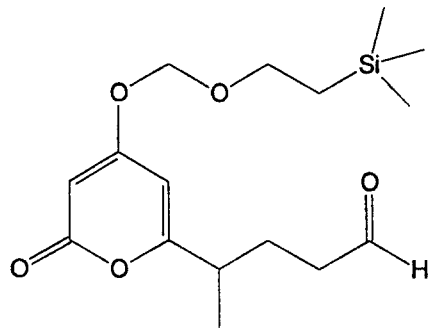
(a) (i) alkylating a pyrone having the structure:



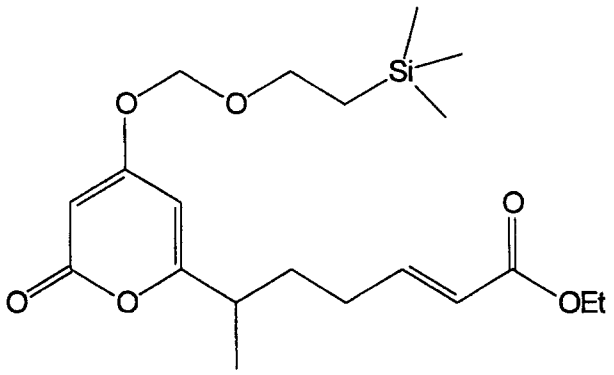
(ii) etherifying the pyrone formed in step (i) under suitable conditions to form protected pyrone having the structure:



(b) (i) hydroborating the protected pyrone formed in step (a)(ii) under suitable basic conditions; and (ii) oxidizing under suitable conditions to form a pyrone aldehyde having the structure:



(c) condensing the pyrone aldehyde formed in step (b)(ii) with triethyl phosphonoacetate under suitable conditions to form a protected pyrone ester having the structure:



and (d) cleaving the protected pyrone ester under suitable conditions to form the pyrone ester.

As practiced in the invention, allylation step (a)(i) is effected using allyl chloride, bromide or fluoride as the halide and a strong base, such as sodium hydride or n-butyl lithium, in a polar aprotic solvent mixture favorably made up of THF and HMPT. Protection step (a)(ii) is carried out using a strong non-nucleophilic base, such as DIPEA or triethylamine, in an inert organic solvent, such as

dichloromethane. Hydroboration (b)(i) is performed with a borane complex, such as BH_3-SMe_2, followed by treatment with hydrogen peroxide and inorganic base, such as NaOH. Oxidation (b)(ii) preferably utilizes standard Swern conditions. Condensation step (c) is performed using a strong non-nucleophilic base such as sodium hydride. Deprotection step (d) is effected using a strong acid such as sulfuric acid in the presence of a protic solvent, such as ethanol, and a miscible aprotic organic solvent, such as THF.

Generally, the Wadsworth-Emmons reaction is applied in the pathway leading to both **1** and **9**, and tolerates the use of aprotic, anhydrous solvents. While both toluene and THF have been used effectively, higher yields are obtained with THF. The preferred base is NaH although other anhydrous bases are also effective. Other reactions generating carbon-carbon double bonds could be equivalently used. Intermediate ester **16** may alternatively be prepared by an addition reaction involving lithium dimethyl cuprate, or an equivalent organometallic reagent. The reductions of the two esters on the pathway to **1** are both performed with DIBAL, although a number of hydride reagents could have been used. Any aprotic, anhydrous solvent would be permissible as long as its melting point is below -78°C. The reaction proceeds rapidly at -78°C, but may optionally be carried out at temperatures up to -40°C without untoward consequences. The oxidations on the pathway to **1** have been efficiently performed both under Swern conditions and with DDQ, or any reagent proficient in the oxidation of allylic alcohols or

primary alcohols, including, but not limited to, manganese oxide, pyridinium chlorochromate, and pyridinium dichromate. The pathway using DDQ is more effective with unsaturated alcohols. The oxidation reaction is preferably performed using a variety of aprotic, anhydrous solvents.

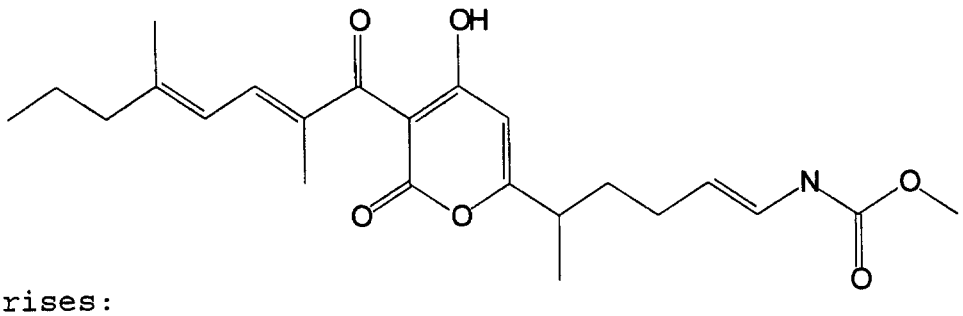
With respect to the production of the pyrone, ethyl propionylacetate is hydroyzed with aqueous NaOH. The reaction may be carried out using any hydroxylic base. The dimerization of the acid to produce pyrone **5** is preferably effected in aprotic, anhydrous solvents. Other carbonyldiimidazole equivalents (*e.g.*, phosphene) can be similarly used. The hydroysis of the propionyl groups to yield **6** occurs in strong acids, including, but not limited to, hydrochloric acid, phosphoric acid, nitric acid. The alkylation of **6** with either 3-bromopropionaldehyde dimethyl acetal or allyl bromide is preferably performed in the presence of hexamethylphosphoric triamide (HMPT) to help solubilize the anion.

The SEM ether is a preferred protecting group. For the installation step, various amine bases may be used, including, but not limited to, diisopropylethylamine (DIPEA), triethylamine, DBU (1,8-diazbicyclo[5.4.0]undec-7-ene), and pyridine. The reaction may be performed in various polar aprotic solvents, including, but not limited to, chloroform, carbon tetrachloride and dimethyl formamide (DMF). The removal of the dimethyl acetal using dilute H_2SO_4 in THF/H_2O may be carried out with mild acids which do not cleave the SEM group. In general, if H_2O is used as a co-solvent rather than an alcohol, the SEM group is not

affected. The removal of the SEM group in intermediate **9** to produce compound **10** is effected using either TBAF/DMPU or dilute H_2SO_4 in THF/EtOH, acidic conditions being the more effective.

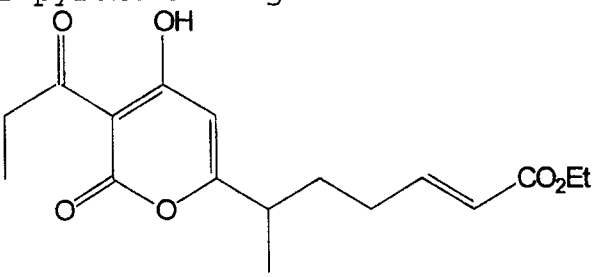
The hydroboration of intermediate **11** is carried out with a number of borane reagents, *e.g.*, $BH_3 \cdot THF$ or borane-dimethyl sulfide complex (Figure 7). Yields are limited by the reactivity of the pyrone under these conditions. The aldol reaction between compounds **1** and **10** is best performed using TFA in CH_2Cl_2. In the alternate route used to attach the 3-position side chain, the acylation of compound **10** with propionyl chloride to produce intermediate **15** proceeds efficiently in the presence of TFA at elevated temperature. Lithium diisopropylamide (LDA) is an efficient base for the aldol reaction of between compounds **14** and **15** yielding intermediate **17**. A variety of other bases are also useful for the purpose, including, but not limited to, hydroxide bases, lithium-containing bases and alkoxides.

The present invention provides a process of preparing a myxopyronin having the structure:

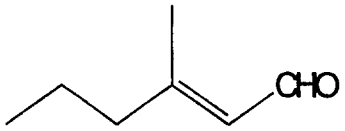


which comprises:

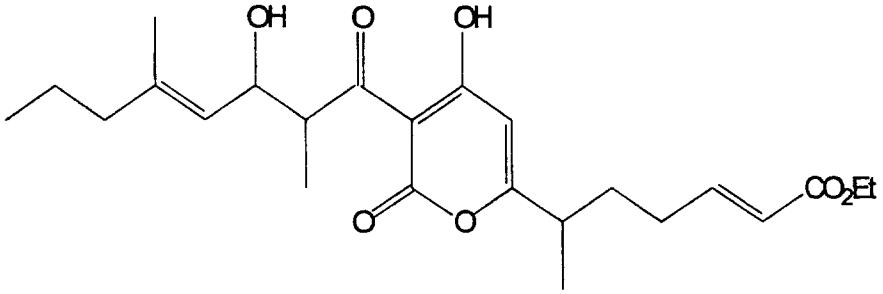
(a) treating an acyl pyrone having the structure:



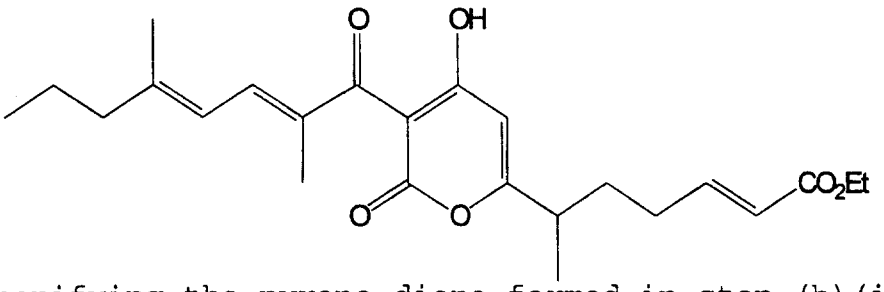
with an unsaturated aldehyde having the structure:



under suitable conditions to form a pyrone aldol having the structure:



(b)(i) mesylating the pyrone aldol formed in step (a) under suitable conditions to form a pyrone aldol mesylate; and (ii) reacting the pyrone aldol mesylate formed in step (b)(i) under suitable basic conditions to form a pyrone diene having the structure:



and (c) saponifying the pyrone diene formed in step (b)(ii) under suitable conditions to form a pyrone acid; (d) converting the pyrone acid formed in step (c) under suitable conditions to a pyrone acyl azide; and (e) solvolyzing the pyrone acyl azide formed in step (d) with methanol under

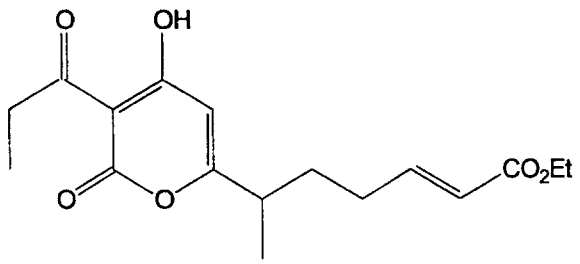
suitable conditions to form the myxopyronin.

In one embodiment, the present invention provides a process as disclosed above wherein the acyl pyrone in step (a) is treated with the unsaturated aldehyde in the presence of a Lewis acid catalyst. In a certain embodiment, the present invention provides the process wherein the acid catalyst is titanium tetrachloride/triethylamine combination. In another embodiment, the present invention provides a process as disclosed above wherein the pyrone aldol in step (b)(i) is mesylated with methanesulfonyl (mesyl) chloride in the presence of triethylamine. In another embodiment, the present invention provides a process as disclosed above wherein the pyrone aldol mesylate in step (b)(ii) is reacted with DBU. In another embodiment, the present invention provides a process as above wherein the pyrone diene in step (c) is saponified with lithium hydroxide. In yet another embodiment, the present invention provides a process as above wherein the pyrone acid in step (d) is converted using diphenylphosphoryl azide in the presence of triethylamine.

The aldol condensation of step (a) may be effected at subambient temperatures, preferably at -78°C. Mesylation step (b)(i) is carried out preferably using mesyl chloride but an equivalent reaction sequence would result using another acylating agent, such as p-tosyl chloride, acetic anhydride. Step (b)(i) occurs efficiently in the presence of a non-nucleophilic organic base, such as DIPEA or triethylamine. Elimination step (b)(ii) may be performed using a reagent effective to cause elimination, preferably,

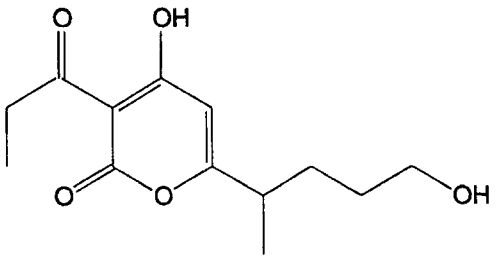
a strong non-nucleophilic base such as DBU. Saponifying step (c) is effected using a base such as lithium hydroxide, sodium hydroxide or potassium hydroxide under aqueous or mixed aqueous/dipolar solvent conditions. Converting step (d) is carried out by heating the pyrone acid with diphenylphosphoryl azide, or an equivalent reagent, in the present of a strong non-nucleophilic base, such as triethylamine or diethylisopropylamine, in a noninteracting organic solvent, such as benzene, toluene or xylene, at a temperature above room temperature, preferably at the reflux temperature of the solvent. Solvolyzing step (e) is effected by heating the pyrone acyl azide in methanol at a temperature above room temperature, preferably at the reflux temperature of methanol.

The present invention provides a process of preparing an acyl pyrone having the structure:



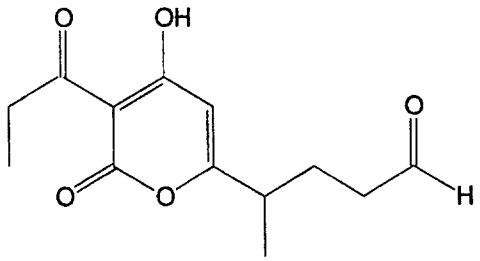
which comprises:

(a) oxidizing a pyrone diol having the structure:



under suitable oxidizing conditions to form a pyrone

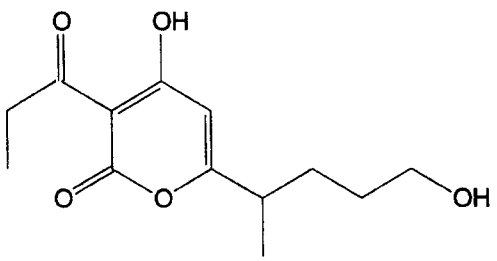
aldehyde having the structure:



and (b) condensing the pyrone aldehyde formed in step (a) with triethylphosphonoacetate under suitable basic conditions to form the pyrone ester. In one embodiment, the present invention provides a process as shown above wherein the pyrone diol in step (a) is oxidized with a Dess-Martin periodinate. In another embodiment, the present invention provides a process as above wherein the condensing step is effected with sodium hydride.

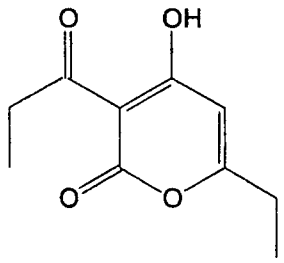
Oxidizing step (a) is carried out using any oxidant known in the art suited to the purpose, including chromium oxide, pyridinium chlorochromate, dicyclohexylcarbodiimide/ dimethylsulfoxidealuminum oxide/acetone, lead tetraacetate, *etc.* A preferred oxidant is the Dess-Martin periodinate. Condensing step (b) is effected in the presence of a strong non-nucleophilic base, such as sodium hydride or potassium t-butoxide, in an inert organic solvent such as benzene, toluene, or xylene, typically at ambient temperatures.

The present invention provides a process of preparing a pyrone diol having the structure:



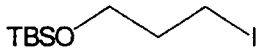
which comprises:

(a)(i) deprotonating an acyl pyrone having the structure:

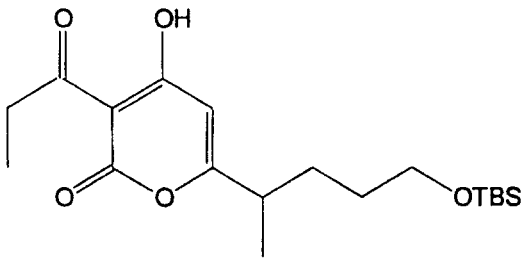


under suitable basic conditions to form an anion; and

(ii) alkylating the anion formed in step (a)(i) with a siloxyalkyl halide having the structure:



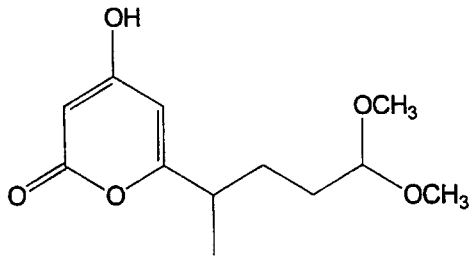
under suitable conditions to form an alkylated pyrone having the structure:

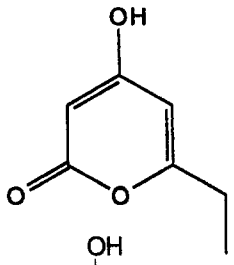


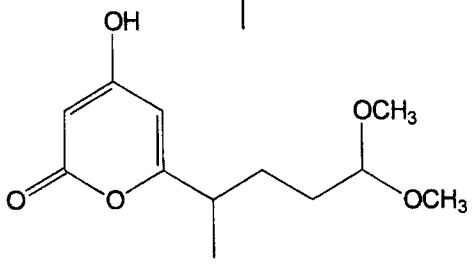
and (b) deprotecting the alkylated pyrone formed in step (a)(ii) under suitable conditions to form the pyrone diol. In one embodiment, the present invention provides a process as disclosed wherein the acyl pyrone in step (a)(i) is deprotonated using lithium diisopropylamide or lithium diethylamide. In another embodiment, the present invention provides a process as above wherein the alkylated pyrone in step (b) is deprotected with a weak acid. In a certain embodiment, the invention provides a process wherein the weak acid is acetic acid.

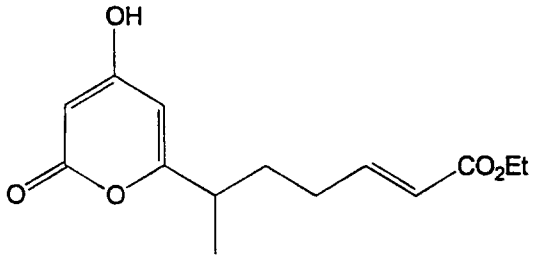
Deprotonating step (a)(i) is carried out using a strong non-nucleophilic base, such as LDA, lithium diethylamide, potassium t-butoxide, sodium amide, sodium hydride, *etc.*, in a non-interacting organic dipolar solvent or solvent mixture, such as tetrahydrofuran (THF) and/or hexamethylphosphoramide (HMPA), at subambient temperatures, preferably at -78°C. The deprotonated dianion is used directly in the alkylation step (a)(ii) is performed at subambient temperatures, preferably -78°C.

The present invention further provides the following compositions of matter, having the structures set forth below. These compounds are useful as intermediates in the synthesis of myxopyronins and corallopyronins according to the present invention:





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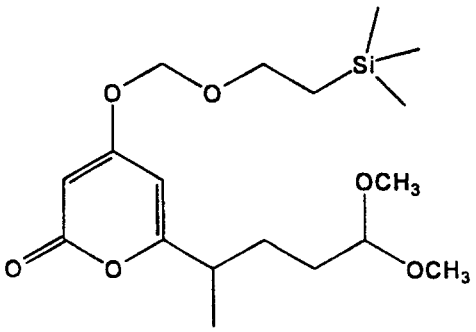
O
CO2Et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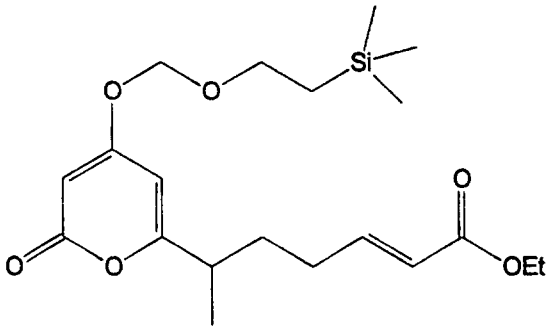
O
OCH3
OCH3
O
O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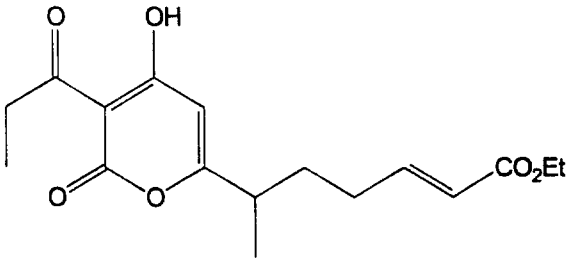
O
O
OEt
O
O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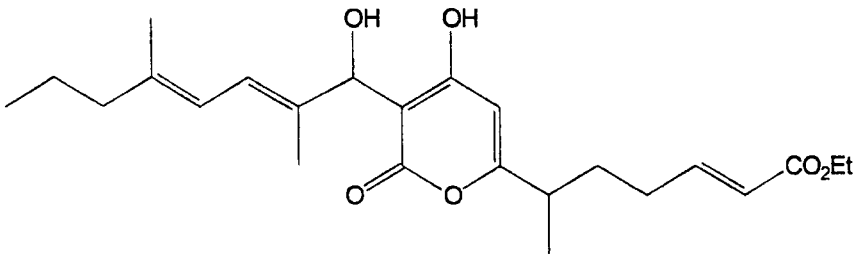
CO2Et
O
O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CO2Et
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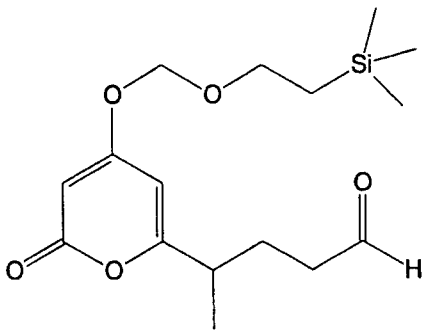
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O
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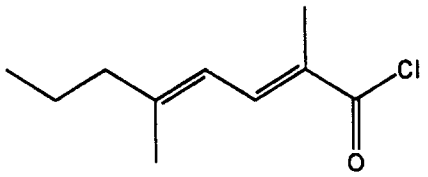
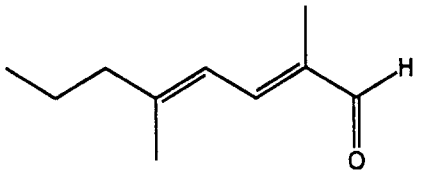
O
O
H


Cl
O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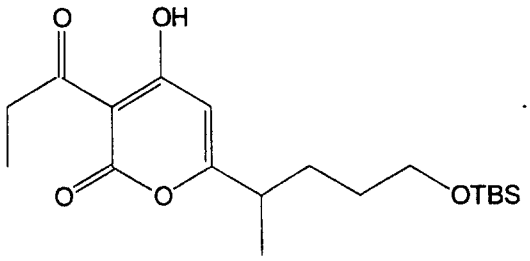
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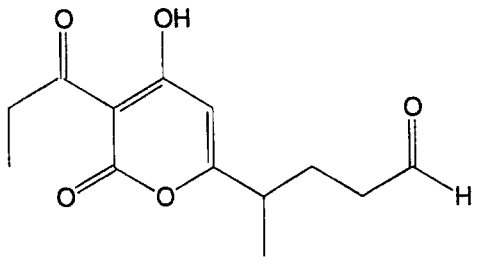
O
OTBS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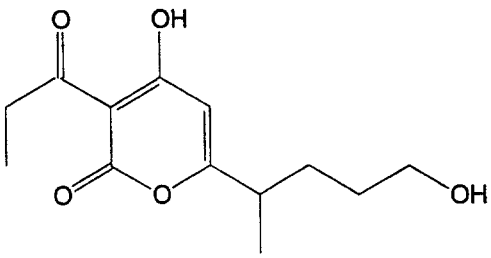
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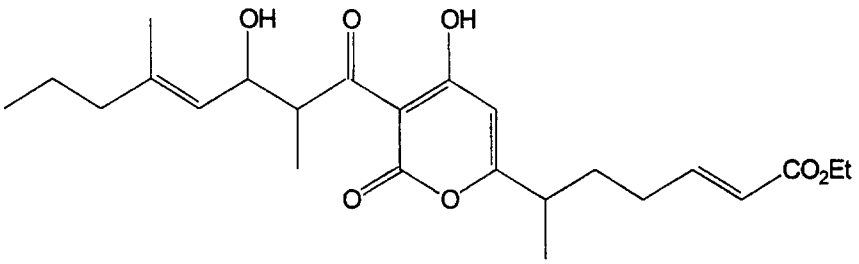

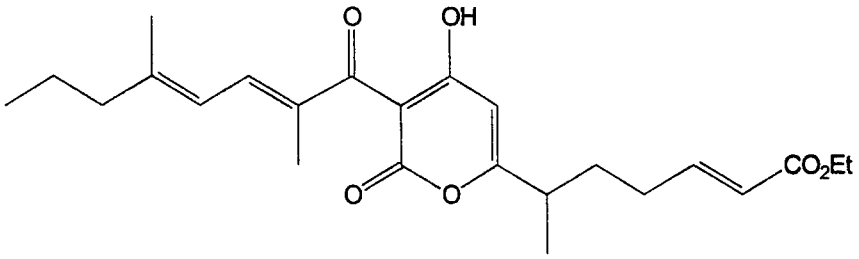

The scope of the present invention includes compositions of matter wherein the C_α carbon at the 6-position of the pyrone ring therein possesses either an R or S absolute configuration, as well as mixtures thereof. The processes of the present invention encompass the use of various alternate protecting groups known in the art. For example, in the preparation of unsaturated aldehyde **1**, ethyl ester **16** may be equivalently replaced with a methyl, propyl, isobutyl, phenyl, or benzyl ester, wherein the triethylphosphonoacetate or triethylphosphonopropionate may be replaced with the corresponding alternate ester. Similarly, in the preparation of intermediate pyrone ester **10** and of

myxopyronin **18**, the ethyl ester may be equivalently replaced with, for example, a methyl, propyl, isobutyl, phenyl, or benzyl ester, wherein the triethylphosphonoacetate used in the conversion from **8** to **9** may be replaced with the corresponding alternate ester. Furthermore, in the conversion from compound **6** to **7**, the bromopropionaldehyde dimethyl acetal may be equivalently replaced with, for example, an ethyl, propyl, butyl, ethylene, or propylene acetal, and in the conversion from **7** to **8**, SEM-Cl may be equivalently replaced with another protecting group, for example, methoxymethyl, methylthiomethyl, trimethylsilyl, t-butyldimethylsilyl, or tetrahydropyranyl.

The present invention will be better understood from the Experimental Details which follow. However, one skilled in the art will readily appreciate that the specific methods and results discussed are merely illustrative of the invention as described in the claims which follow thereafter.

EXAMPLE 1

Synthesis of 6-ethyl pyrone

Hydrolysis of the ethyl propionylacetate **4**

To a flame-dried flask under flushing argon containing 25 gr (175 mmol) of ethyl propionylacetate **4** was added 300 ml of 1.5M NaOH. The solution was stirred at room temperature for 18 hours. Tlc indicated that the starting material was gone. The solution was placed in an ice/H_2O bath and concentrated

HCl was added until the pH of the solution was 1. The reaction was allowed to warm to room temperature. The solution was saturated with KCl and extracted with EtOAc (3x100 ml) and $CHCl_3$ (3x100 ml). The combined organic layers were dried with Na_2SO_4, filtered and evaporated on a rotary evaporator. This yielded 15.5 gr (76%) of a white solid. The product needed no further purification and was used directly in the next step.

^1H NMR (300MHz, $CDCl_3$): δ 1.1 (3H, t); 2.6 (2H, q); 3.5 (2H, s).

Dimerization of the acid to produce the pyrone **5**

To a flame-dried flask under flushing argon containing 10.55 gr (91 mmol, 1 eq) of the acid dissolved in 250 ml of freshly distilled THF was added 16.22 gr (100 mmol, 1.1 eq) of carbonyldiimidazole. The reaction was left to stir for 12 hours. The reaction was concentrated using a rotary evaporator. The residue was partitioned between 100 ml of $CHCl_3$ and 100 ml of 10% HCl. The aqueous layer was extracted with $CHCl_3$ (2x 50 ml). The combined organic layers were dried with Na_2SO_4, filtered and evaporated on a rotary evaporator. The product needed no further purification as long as it was left on a vacuum pump long enough to remove any remaining starting acid. This yielded 8.8 gr (98%) of **5** a tan solid.

^1H NMR (300MHz, $CDCl_3$): δ 1.15 (3H, t); 1.25 (3H, t); 2.55 (2H, q); 3.1 (2H, q); 5.95 (1H, s).

Removal of the propionoyl group to produce 6

In a round-bottomed flask was placed 11.4 gr (58.2 mmol, 1 eq) of the pyrone **5** and it was dissolved in 50 ml of concentrated H_2SO_4. The solution was heated to 130°C in an oil bath for 15 minutes. The reaction was allowed to cool to room temperature. Approximately 50 gr of ice was added with stirring. The solution was extracted with Et_2O (3x 50 ml). The combined organic layers were dried with Na_2SO_4, filtered and evaporated on a rotary evaporator. This yielded 7.7 gr (94%) of **6** a tan solid. The product needed no further purification.

^1H NMR (300MHz, $CDCl_3$): δ 1.2 (3H, t); 2.5 (2H, q); 5.65 (1H, d); 6.0 (1H, d).

EXAMPLE 2

Construction of 6-position side chain

3-Bromopropionaldehyde dimethyl acetal approach: Alkylation of pyrone with 3-bromopropionaldehyde dimethyl acetal to produce 7

To a flame-dried flask under flushing argon containing 2.5 gr (18 mmol, 1 eq) of the ethyl pyrone **6** dissolved in 40 ml of freshly distilled THF was added 8 ml of HMPT. The solution was slowly cooled to -78°C in a dry ice/acetone bath, making sure the ethyl pyrone stayed in solution. Once the temperature had equilibrated, 24.6 ml (39 mmol, 2.2 eq)

of 1.6 M n-BuLi was added by syringe. The solution quickly became a maroon color. The dry ice/acetone bath was replaced with an ice/H_2O bath and the solution allowed to stir for 30 minutes. At this point, the 3-bromopropionaldehyde dimethyl acetal was added by syringe. The solution was left to stir and warm to room temperature overnight. The reaction was quenched by the addition of 25 ml of H_2O. Addition of 1% HCl occurred until the solution was acidic. The solution was extracted with Et_2O (3x 50ml). The combined organic layers were extracted with saturated brine solution, dried with Na_2SO_4, filtered and evaporated on a rotary evaporator. The product was **7** a brown oil (1.75 gr) and was not purified at this time. It was used directly in the produciton of the SEM ether.

Conversion of the 4-hydroxyl group of **7** into the SEM ether **8**

To a flame-dried flask under flushing argon containing 1.75 gr (12 mmol, 1 eq) of the crude alkylation product **7** dissolved in 40 ml of anhydrous CH_2Cl_2 was added 2.42 ml (12 mmol, 1 eq) of N,N-diisopropylethylamine (DIPEA) by syringe. The solution immediately becomae orange. The solution was cooled with a ice/H_2O bath and 2.46 ml (12 mmol, 1 eq) of 2-(trimethylsilyl)ethoxymethyl chloride (SEM-Cl) was added by syringe. A white vapor formed. The reaction was allowed to stir for 2 hours at which time tlc showed that no starting material remained (5:2 benzene/ ethyl acetate). The reaction was diluted with 150 ml of Et_2O and the resulting solution

extracted with saturated $NaHCO_3$ (2x 50 ml). The organic layer was extracted with brine solution (1x 50 ml). The organic layer was dried with Na_2SO_4, filtered and evaporated on a rotary evaporator. The residue was placed on a SiO_2 column and eluted with 5:2 benzene/ ethyl acetate. This yielded 0.46 gr (7% for the two steps combined) of a light yellow oil **8**.

^1H NMR (300MHz, $CDCl_3$): δ_0.0 (9H, s); 1.0 (2H, t); 1.2 (3H, d); 1.5-1.8 (4H, m); 2.5 (1H, m); 3.3 (6H, 2s); 3.7 (2H, t); 4.3 (1H, t); 5.2 (2H, s); 5.6 (1H, d); 5.8 (1H, d).

Deprotection of the aldehyde

In a round-bottomed flask was placed 0.45 gr (1.2 mmol, 1 eq) of the pyrone **8** and it was dissolved in 22 ml of a 10:1 mixture of THF/H_2O. To this solution was added 10 drops of concentrated H_2SO_4 and the reaction left to stir. After 3 hours, 3 more drops of H_2SO_4 were added. After 3 additional hours, tlc showed no more starting material (5:2 benzene/ethyl acetate). The reaction was diluted with 20 ml of Et2O and this solution extracted with saturated $NaHCO_3$ (1x 10 ml) and brine (1x 10 ml). The organic layer was dried with Na_2SO_4, filtered and evaporated on a rotary evaporator. This yielded 0.39 gr (>98%) of a light yellow oil **12**. The product needed no further purification.

^1H NMR (300MHz, $CDCl_3$): δ 0.0 (9H, s); 1.0 (2H, t); 1.2 (3H, d); 1.8-2.0 (4H, m); 2.6 (1H, m); 3.7 (2H, t); 5.2 (2H, s); 5.6 (1H, d); 5.8 (1H, d) 9.75 (1H, t).

Horner-Emmons-Wadsworth reaction of the deprotected aldehyde to produce 9

To a flame-dried flask under flushing argon containing 0.236 ml (1.2 mmol, 1 eq) of the triethyl phosphonoacetate dissolved in 15 ml of freshly distilled toluene was added 50 mg (1.24 mmol, 1.05 eq) of NaH as a 60% mineral oil dispersion. Hydrogen evolution was witnessed. Once this subsided, 0.40 gr (1.2 mmol, 1 eq) of the aldehyde dissolved in toluene (3 ml) was added by syringe. The syringe was washed with an additional 2 ml of toluene and the solution added to the reaction. Almost immediately, an orange oil came out of solution. The reaction was left to stir overnight. The reaction was stopped by the addition of 20 ml of H_2O and the solution made acidic with 1% HCl. The solution was extracted with Et_2O (3x10 ml). The combined organics were extracted with saturated $NaHCO_3$ (1x 10ml) and brine (1x 10ml). The organic layer was dried with Na_2SO_4, filtered and evaporated on a rotary evaporator. The residue was placed on a SiO_2 column and eluted with 2:1 hexane/ ethyl acetate. This yielded 0.347 gr (74%) of a clear oil **9**. ^1H NMR (300MHz, $CDCl_3$): δ 0.0 (9H, s); 0.9 (2H, t); 1.25 (3H, d); 1.25 (3H, t); 1.6 (2H, m); 1.9 (1H, m); 2.2 (2H, m); 2.6 (1H, m); 3.7 (2H, t); 4.2 (2H, q); 5.2 (2H, s); 5.6 (1H, d); 5.8 (1H, d); 5.85 (1H, d); 6.9 (1H, dt).

EXAMPLE 3

Allyl bromide approach:

Allylation of ethyl pyrone 6

To a flame-dried flask under flushing argon containing 0.108 gr (0.77 mmol, 1 eq) of the ethyl pyrone **6** dissolved in 20 ml of freshly distilled THF was added 2 ml of HMPT. The solution was slowly cooled to -78°C in a dry ice/ acetone bath, making sure the ethyl pyrone stayed in solution. Once the temperature had equilibrated, 1.06 ml (1.7 mmol, 2.2 eq) of 1.6 M n-BuLi was added by syringe. The solution quickly became a maroon color. The dry ice/acetone bath was replaced with an ice/H_2O bath and the solution allowed to stir for 2 hours. At this point, the allyl bromide was added by syringe. As the end of the addition was reached, the color of the solution became almost yellow. The reaction was allowed to stir for 1 hour. The contents of the reaction were partitioned between Et_2O and 1N HCl (25 ml of each). The layers were separated and the aqueous was extracted with Et_2O (2x 25ml). The organics were combined and extracted with 25 ml of saturated KCl. The organic layer was dried with Na_2SO_4, filtered and evaporated on a rotary evaporator. This yielded 0.110 gr (76%) of a light yellow oil. The product needed no further purification.

^1H NMR (300MHz, $CDCl_3$): δ 1.2 (3H, d); 2.25 (1H, m); 2.45 (1H, m); 2.6 (1H, m); 5.0 (1H, s); 5.05 (1H, d); 5.6 (1H, d);5.7 (1H, m); 5.9 (1H, d).

Conversion of the 4-hydroxyl group into the SEM ether **11**

To a flame-dried flask under flushing argon containing 0.110

gr (0.61 mmol, 1 eq) of the crude alkylation product dissolved in 3 ml of anhydrous CH_2Cl_2 was added 0.106 ml (0.61 mmol, 1 eq) of N,N-diisopropylethylamine (DIPEA) by syringe. The solution immediately becomae orange. The solution was cooled with a ice/H_2O bath and 0.108 ml (0.61 mmol, 1 eq) of 2-(trimethylsilyl)ethoxymethyl chloride (SEM-Cl) was added by syringe. A white vapor formed. The reaction was allowed to stir for 2 hours at which time tlc showed that no starting material remained (3:1 hexane/ ethyl acetate). The reaction was diluted with 15 ml of Et_2O and the resulting solution extracted with saturated $NaHCO_3$ (2x 5 ml). The organic layer was extracted with brine solution (1x 5 ml). The organic layer was dried with Na_2SO_4, filtered and evaporated on a rotary evaporator. The residue was placed on a SiO_2 column and eluted with 3:1 hexane/ ethyl acetate. This yielded 0.83 gr (45%) of a clear oil **11**.

^1H NMR (300MHz, $CDCl_3$): δ 0.0 (9H, s); 0.9 (2H, t); 1.2 (3H, d); 2.25 (1H, m); 2.45 (1H, m); 2.6 (1H, m); 3.7 (2H, t); 4.2 (2H, q); 5.0 (1H, s); 5.05 (1H, d); 5.2 (2H, s); 5.6 (1H, d);5.7 (1H, m); 5.8 (1H, d).

Hydroboration of the allyl group

To a flame-dried flask under flushing argon containing 0.74 gr (2.4 mmol, 1 eq) of the allylation product **11** dissolved in 20 ml of freshly distilled THF and cooled to 0°C in an ice/H_2O bath was added 1.25 ml (2.5 mmol, 1.05 eq) of BH_3THF by syringe. The reaction was allowed to stir for two hours at which time tlc indicated the reaction was finished. The

reaction was stopped by sequential addition of 8 ml of methanol, 3 ml of 5M NaOH and 3 ml of 30% H_2O_2. The solution was acidified to pH 4 with 1% HCl and extracted with Et_2O (3x20 ml). The combined organic layers were dried with Na_2SO_4, filtered and evaporated on a rotary evaporator. The residue was placed on a SiO_2 column and eluted with 2:1 ethyl acetate/ toluene. This yielded 0.30 gr (38%) of a clear oil.

^1H NMR (300MHz, $CDCl_3$): δ 0.0 (9H, s); 0.9 (2H, t); 1.25 (3H, d); 1.5-1.8 (4H, m); 2.55 (1H, m); 2.45 (1H, m); 2.6 (1H, m); 3.65 (2H, t); 3.75 (2H, t); 5.2 (2H, s); 5.6 (1H, d); 5.8 (1H, d).

Swern oxidation of the alcohol to produce **12**

A flame-dried flask under flushing argon containing 0.105 ml (1.5 mmol, 2.55 eq) of DMSO dissolved in 5 ml of anhydrous CH_2Cl_2 was cooled to -78°C in a dry ice/acetone bath. To this solution was added 0.058 ml (0.64 mmol, 1.14 eq) of oxalyl chloride by syringe. The solution was allowed to stir for 5 minutes. 0.19 gr (0.58 mmol, 1 eq) of the alcohol dissolved in 5 ml of anhydrous CH_2Cl_2 was added to the solution slowly over the course of 5 minutes. The solution was allowed to stir for 30 minutes. The reaction was terminated by the addition of 0.209 ml (1.5 mmol, 2.6 eq) of triethylamine and stirring for 5 minutes before allowing the solution to warm to room temperature. The solution was diluted with 10 ml of H_2O and the aqueous and organic layers separated. The aqueous layer was extracted with CH_2Cl_2 (2x10 ml). The

combined organic layers were dried with Na_2SO_4, filtered and evaporated on a rotary evaporator. The residue was placed on a SiO_2 column and eluted with 2:1 toluene/ethyl acetate. This yielded 0.15 gr (80%) of a clear oil **12**. ^1H NMR showed this compound identical to the aldehyde prepared using the 3-bromopropionaldehyde dimethyl acetal pathway.

Horner-Emmons-Wadsworth reaction of the aldehyde

To a flame-dried flask under flushing argon in an ice/H_2O bath containing 0.223 gr (1.1 mmol, 1.05 eq) of the triethyl phosphonoacetate dissolved in 15 ml of freshly distilled THF was added 45 mg (1.1 mmol, 1.05 eq) of NaH as a 60% mineral oil dispersion. Once hydrogen evolution subsided, the aldehyde dissolved in THF (3 ml) was added by syringe. The syringe was washed with an additional 2 ml of THF and the solution added to the reaction. Almost immediately, an orange oil came out of solution. The reaction was left to stir overnight. The reaction was quenched by the addition of 20 ml of H_2O and the solution made acidic with 1% HCl. The solution was extracted with Et_2O (3x10 ml). The combined organics were extracted with saturated $NaHCO_3$ (1x10ml) and brine (1x10ml). The organic layer was dried with Na_2SO_4, filtered and evaporated on a rotary evaporator. The residue was placed on a SiO_2 column and eluted with 2:1 hexane/ethyl acetate. This yielded 0.39 gr (92%) of a clear oil. ^1H NMR showed this compound identical to the HEW adduct prepared using the 3-bromopropionaldehyde dimethyl acetal pathway.

Removal of the SEM protecting group to produce **10**

In a round-bottomed flask was placed 0.55 gr (1.4 mmol, 1 eq) of the pyrone and it was dissolved in 33 ml of a 10:1 mixture of THF/EtOH. To this solution was added 30 drops of concentrated H_2SO_4 and the reaction left to stir. After 6 hours, tlc indicated no starting material. The reaction was diluted with 30 ml of ethyl acetate. The solution was extracted with saturated $NaHCO_3$ (3x20 ml). The aqueous layer was acidified to <pH 4 with 10 % HCl. The solution was extracted with ethyl acetate (3x 30ml). The combined organic layers were dried with Na_2SO_4, filtered and evaporated on a rotary evaporator. This yielded 0.37 gr (>98%) of a clear oil **10**. The product needed no further purification.

^1H NMR (300MHz, $CDCl_3$): δ 1.25 (3H, d); 1.25 (3H, t); 1.7 (1H, m); 1.9 (1H, m); 2.2 (2H, m); 2.6 (1H, m); 4.2 (2H, q); 5.5 (1H, d); 5.8 (1H, d); 5.95 (1H, d); 6.9 (1H, dt).

EXAMPLE 4

Synthesis of the 3-position sidechain:

Horner-Emmons-Wadsworth reaction of 2-pentanone with triethyl phosphonoacetate

To a flame-dried flask under flushing argon in an ice/H_2O bath containing 7.48 ml (37.7 mmol, 1. eq) of the triethyl phosphonoacetate dissolved in 100 ml of freshly distilled toluene was added 0.95 gr (40 mmol, 1.05 eq) of NaH as a 60% mineral oil dispersion. Once hydrogen evolution subsided,

2-pentanone was added. Almost immediately, an orange oil came out of solution. The reaction was left to stir overnight. The reaction was quenched by the addition of 50 ml of H_2O and the solution made acidic with 1% HCl. The solution was extracted with Et_2O (3x20 ml). The combined organics were extracted with saturated $NaHCO_3$ (1x10ml) and brine (1x10ml). The organic layer was dried with Na_2SO_4, filtered and evaporated on a rotary evaporator. The residue was placed on a SiO_2 column and eluted with 15:1 hexane/ ethyl acetate. This yielded 4.9 gr (83%) of a clear oil. ^1H NMR (300MHz, $CDCl_3$): δ 0.9 (3H, t); 1.25 (3H, t); 1.5 (2H, m); 2.1 (2H, t) 2.15 (3H, s); 4.15 (2H, q); 5.65 (1H, s).

Alternate synthesis of the unsaturated ester **16**

To a flask containing 45.7 gr (240 mmol, 1 eq) of CuI suspended in 240ml of diethyl ether cooled to 0°C with an ice/H_2O bath was added 343 ml (480 mmol, 2 eq) of a 1.4M solution of MeLi over the course of 1 hour. The solution was stirred for 5 minutes at 0°C and then cooled to -78 C with a dry ice/acetone bath. Initially, a yellow precipitate formed upon the addition of the MeLi but it solubilized with time.

In a second flask, 18.98 gr (120 mmol, 1 eq) of ethylbutyryl acetate in 160 ml of diethyl ether was added to a suspension of 5.28 gr (132 mmol, 1.1 eq) of NaH in 80 ml of diethyl ether cooled to 0°C over the course of 1 hour. The slurry that formed was stirred for 20 minutes at 0°C. 19.1 ml (132

mmol, 1.1. eq) of diethylphosphorochloridate was added over the course of 10 minutes. The solution was stirred at room temperature for 2 hours and then poured into 200 ml of ice/saturated NH_4Cl. The aqueous and organic layers were separated. The organic layer was washed with 300 ml of saturated $NaHCO_3$. The organic layer was dried with Na_2SO_4, filtered and evaporated on a rotary evaporator. This yielded the 35.4 gr of the enol phosphonate which was used without further purification. The enol phosphonate was dissolved in 120 ml of diethyl ether and added to the first flask containing $LiMe_2Cu$ over the course of 20 minutes with the solution was being cooled to -78°C. The solution was stirred for 2.5 hours while being cooled at -78°C. The solution was poured into 300 ml of saturated NH_4Cl. The aqueous and organic layers were separated. The organic layer was washed with 2x200 ml of saturated $NaHCO_3$ and 300 ml of brine solution. The organic layer was dried with Na_2SO_4, filtered and evaporated on a rotary evaporator. This yielded 17 gr of a light green liquid that was distilled to give 10.4 gr (55%) yield of a colorless oil. The NMR was identical to that of **16** but contained a 10:1 ratio of E/Z isomers.

DIBAL reduction of the ethyl ester

A flame-dried flask under flushing argon containing 4.9 gr (31.4 mmol, 1 eq) of the ethyl ester dissolved in 100 ml of freshly distilled THF was cooled to -78°C with a dry ice/acetone bath. 78.5 ml (78.5 mmol, 2.5 eq) of a 1.0M

solution of DIBAL was dripped into the solution by syringe over the course of 10 minutes. The solution was left to stir for 1 hour. Fifty milliliters of methanol were poured into the solution to quench the excess DIBAL. The solution was diluted with 200 ml of H_2O. 200 ml of Et_2O was added to the solution followed by 100 ml of 5% HCl. The whole solution was poured into a separatory funnel and the aqueous and organic layers separated. The aqueous layer was extracted with Et_2O (2x50 ml). The combined organic layers were dried with Na_2SO_4, filtered and evaporated on a rotary evaporator. The residue was placed on a SiO_2 column and eluted with 3:1 hexane/ethyl acetate. This yielded 1.2 gr (34%) of a clear oil.

^1H NMR (300MHz, $CDCl_3$): δ 0.85 (3H, t); 1.4 (2H, m); 1.65 (3H, s); 1.9 (2H, t); 4.1 (2H, d); 5.4 (1H, t).

Swern oxidation of the alcohol to produce **14**

A flame-dried flask under flushing argon containing 1.9 ml (26.8 mmol, 2.55 eq) of DMSO dissolved in 30 ml of anhydrous CH_2Cl_2 was cooled to -78°C in a dry ice/acetone bath. To this solution was added 1.05 ml (12 mmol, 1.14 eq) of oxalyl chloride by syringe. The solution was allowed to stir for 5 minutes. 1.2 gr (10.5 mmol, 1 eq) of the alcohol dissolved in 10 ml of anhydrous CH_2Cl_2 was added to the solution slowly over the course of 5 minutes. The syringe was washed with 10 ml of CH_2Cl_2 and this solution added to the reaction. The solution was allowed to stir for 30 minutes. The reaction

was stopped by the addition of 3.81 ml (27.3 mmol, 2.6 eq) of triethylamine and stirring for 5 minutes before allowing the solution to warm to room temperature. The solution was diluted with 20 ml of H_2O and the aqueous and organic layers separated. The aqueous layer was extracted with CH_2Cl_2 (2x10 ml). The combined organic layers were extracted with brine solution, dried with Na_2SO_4, filtered and evaporated on a rotary evaporator. The residue was placed on a SiO_2 column and eluted with 2:1 toluene/ethyl acetate. This yielded 0.45 gr (38%) of a clear oil **14**.

^1H NMR (300MHz, $CDCl_3$): δ 0.9 (3H, t); 1.55 (2H, m); 2.15 (3H, s); 2.2 (2H, t); 5.9 (1H, d); 10.0 (1H, d).

Horner-Emmons-Wadsworth reaction of **14** with triethyl 2-phosphonopropionate

To a flame-dried flask under flushing argon in an ice/H_2O bath containing 0.86 ml (4.0 mmol, 1 eq) of the triethyl 2-phosphonopropiontate dissolved in 100 ml of freshly distilled toluene was added 0.10 gr (4.2 mmol, 1.05 eq) of NaH as a 60% mineral oil dispersion. Once hydrogen evolution subsided, the aldehyde **14** was added. Almost immediately, an orange oil came out of solution. The reaction was left to stir overnight. The reaction was stopped by the addition of 20 ml of H_2O and the solution made acidic with 10% HCl. The solution was extracted with Et_2O (3x20 ml). The combined organics were extracted with saturated $NaHCO_3$ (1x10ml) and brine (1x10ml). The organic layer was dried with Na_2SO_4, filtered and evaporated on a

rotary evaporator. The residue was placed on a SiO_2 column and eluted with 11:1 hexane/ethyl acetate. This yielded 0.385 gr (50%) of a clear oil.

^1H NMR (300MHz, $CDCl_3$): δ 0.9 (3H, t); 1.3 (3H, t); 1.5 (2H, m); 1.85 (3H, s); 1.95 (3H, s); 2.15 (2H, t) 4.15 (2H, q); 6.1 (1H, d); 7.5 (1H, d).

DIBAL reduction of the ethyl ester

A flame-dried flask under flushing argon containing 1.86 gr (9.5 mmol, 1 eq) of the ethyl ester dissolved in 40 ml of freshly distilled THF was cooled to -78°C with a dry ice/ acetone bath. 23.7 ml (23.7 mmol, 2.5 eq) of a 1.0M solution of DIBAL was dripped into the solution by syringe over the course of 5 minutes. The solution was left to stir for 2 hours. An additional 5 ml of DIBAL was added. One hour later, 20 ml of methanol was poured into the solution to quench the excess DIBAL. The solution was diluted with 50 ml of H_2O. Fifty milliliters of Et_2O were added to the solution followed by 25 ml of 5% HCl. The whole solution was poured into a separatory funnel and the aqueous and organic layers separated. The aqueous layer was extracted with Et_2O (2x20 ml). The combined organic layers were dried with Na_2SO_4, filtered and evaporated on a rotary evaporator. The residue was placed on a SiO_2 column and eluted with 3:1 hexane/ethyl acetate. This yielded 1.32 gr (91%) of a clear oil.

^1H NMR (300MHz, $CDCl_3$): δ 0.9 (3H, t); 1.45 (2H, m); 1.75

(3H, s); 1.8 (3H, s); 2.05 (2H, t); 4.1 (2H, d); 6.0 (1H, d); 6.25 (1H, d).

DDQ oxidation of the alcohol to the aldehyde **1**

To a flame-dried flask under flushing argon containing 0.7576 gr (4.9 mmol, 1 eq) of the alcohol dissolved in 25 ml of freshly distilled THF was added 2.26 gr (25 mmol, 2 eq) of DDQ. The reaction was allowed to stir for 2 hours. At this point, 5 gr of SiO_2 were added and the volatiles evaporated on a rotary evaporator. The resulting solid was placed on top of a SiO_2 column and the product eluted with 7:1 hexanes/ethyl acetate. This yielded 0.39 gr (52%) of a clear oil **1**.

^1H NMR (300MHz, $CDCl_3$): δ 0.9 (3H, t); 1.55 (2H, m); 1.85 (3H, s); 1.95 (3H, s); 2.2 (2H, t) 6.3 (1H, d); 7.1 (1H, d); 9.45 (1H, s).

EXAMPLE 5

Attachment of the 3-position side chain:
Acid-catalyzed aldol reaction between pyrone **10** and aldehyde

To a flame-dried flask under flushing argon containing 0.172 gr (650 μmol, 1 eq) of the pyrone **10** dissolved in 20 ml of anhydrous CH_2Cl_2 was added 34 μl (325 μmol, 0.5 eq) of TFA along with 1 gr of 4Å sieves. The reaction was allowed to stir for 5 minutes. At this point, 100 μl (650 μl, 1 eq) of the aldehyde **1** was added. The reaction was capped and

heated at 45°C for 24 hours. An additional equivalent of TFA was added along with 2 ml of CH_2Cl_2. The reaction was heated for an additional 12 hours. The reaction was filtered. One gram of SiO_2 was added to the solution and the solvent evaporated. The product became adsorbed onto the SiO_2. The resulting solid was applied to the top of a SiO_2 column and eluted successively with 7:1 hexane/ethyl acetate, 2:1 hexane/ethyl acetate, 10:1 ethyl acetate/chloroform with 2 drops of acetic acid for every 6 ml of eluent. This yielded 45 mg of the aldehyde, 1.5 mg of the product (1%) **13** and 75 mg of the pyrone.

^1H NMR (300MHz, $CDCl_3$): δ 0.85 (3H, t); 1.2 (3H, d); 1.25 (3H, t); 1.55 (2H, m); 1.65 (1H, m); 1.7 (3H, s); 1.75 (3H, s); 1.9 (1H, m); 2.05 (2H, t); 2.15 (2H, t); 2.55 (1H, m); 4.15 (2H, q); 5.4 (1H, d); 5.5 (1H, d); 5.75 (1H, s); 5.8 (1H, d); 6.2 (1H, s); 6.9 (1H, m).

Acylation of pyrone **10** with propionyl chloride

To a flame-dried flask under flushing argon containing 35 mg (130 μmol, 1 eq) of the pyrone **10** dissolved in 1 ml of anhydrous TFA was added 23 μl (260 μmol, 2 eq) of propionyl chloride. The reaction was heated to 50°C for 1 hour. An additional 4 equivalents of propionyl chloride were added and the reaction was heated for 12 hours. An additional 4 equivalents of propionyl chloride were added and the reaction was heated for 3 hours. The reaction was partitioned between H_2O and ethyl acetate. The aqueous layer was extracted again with ethyl acetate and the organic

layers were combined. The combined organic layers were dried with Na_2SO_4, filtered and evaporated on a rotary evaporator. The residue was placed on a SiO_2 column and eluted with 2:1 hexane/ethyl acetate. This yielded 21 mg (50%) of a light orange oil **15**.

^1H NMR (300MHz, $CDCl_3$): δ 1.15 (3H, t); 1.25 (3H, d); 1.25 (3H, t); 1.7 (1H, m); 1.9 (1H, m); 2.2 (2H, q); 2.6 (1H, m); 3.1 (2H, q); 4.2 (2H, q); 5.8 (1H, d); 5.95 (1H, s); 6.9 (1H, dt).

Base-catalyzed aldol reaction between pyrone and aldehyde to produce 17

To a flame-dried flask in a -78°C dry ice/ acetone bath under flushing argon containing 21 mg (65 μmol, 1 eq) of the pyrone **15** dissolved in 3 ml of freshly distilled THF was added 2.9 ml (230 μmol, 3.6 eq) of 0.08M LDA by syringe. The reaction went from a light orange to a dark orange. The reaction was allowed to stir for 30 minutes. The aldehyde was added by syringe. The color of the solution became just a little lighter. After stirring for 90 minutes, the reaction was quenched by addition of saturated NH_4Cl solution. Ten milliliters of ethyl acetate were added to dilute the solution. 1% HCl solution was used to make the solution acidic. The aqueous and organic layers were separated. The aqueous layer was extracted with ethyl acetate (2x5 ml). The combined organic layers were dried with Na_2SO_4, filtered and evaporated on a rotary evaporator.

The residue was placed on a SiO_2 column and eluted with 4:4:1 hexane/ ethyl acetate/ methanol. This yielded 2 mg (8%) of a light yellow oil **17**.

^1H NMR (300MHz, $CDCl_3$): δ 0.9 (3H, t); 1.25 (3H, d); 1.25 (3H, t); 1.5 (2H, m); 1.7 (1H, m); 1.85 (3H, t); 1.9 (1H, m); 1.95 (3H, t); 2.15 (2H, t); 2.2 (2H, t); 2.6 (1H, m); 4.2 (2H, q); 5.8 (1H, d); 5.95 (1H, s); 6.15 (1H, d); 6.9 (1H, dt); 7.0 (1H, d).

Hydrolysis of the ester **17** to the acid

To a round-bottomed flask containing 4.0 mg (10μmol, 1 eq) of the pyrone ester **17** dissolved in 5 ml of 2:2:1 methanol/THF/H_2O is added 4 mg (100 μmol, 10 eq) of LiOH H_2O. The solution is stirred at room temperature for 6 hours. The volatiles are evaporated on the rotary evaporator. Any remaining base is quenched by the addition of 1% HCl solution. The aqueous solution is extracted with ethyl acetate (3x10 ml). The combined organic layers are dried with Na_2SO_4, filtered and evaporated on a rotary evaporator. 2 mg of an oily yellow residue is isolated and the residue is used in the next step without any further purification. ^1H NMR (300MHz, $CDCl_3$): δ 0.9 (3H, t); 1.25 (3H, d); 1.5 (2H, m); 1.7 (1H, m); 1.85 (3H, t); 1.9 (1H, m); 1.95 (3H, t); 2.15 (2H, t); 2.2 (2H, t); 2.6 (1H, m); 5.8 (1H, d); 5.95 (1H, s); 6.15 (1H, d); 6.95 (1H, dt); 7.0 (1H, d).

Curtius sequence

To a flame-dried flask under flushing argon containing 2 mg (5.4 μmol, 1 eq) of the residue from the hydrolysis dissolved in 1 ml of acetone is added 1.8 μl (13 μmol, 2.4 eq) of DIPEA. The solution is cooled to 0°C using an ice/H_2O bath. A solution of 0.83 μl (11 μmol, 2 eq) of methyl chloroformate dissolved in acetone is added dropwise over 30 minutes. After the reaction stirs for 30 minutes, a solution of 1.4 mg (2.2 mmol, 4.0 eq) of NaN_3 dissolved in H_2O was added. The solution is stirred for 15 minutes and then poured into 30 ml of ice H_2O. The acyl azide is extracted with 6-2 ml portions of toluene. The combined organic layers are dried with Na_2SO_4, filtered and concentrated to 2 ml on a rotary evaporator. This solution is added slowly over the course of 15 minutes to a vigorously refluxing solution of 250 μl of methanol in 1 ml dry toluene. Reflux is maintained for 30 minutes and the volatiles are evaporated on a rotary evaporator. The residue is placed on a SiO_2 prep plate and eluted with 95:5 CH_2Cl_2/methanol. This yields 0.5 mg of a light yellow oil **18**.

^1H NMR (300MHz, $CDCl_3$): δ 0.9 (3H, t); 1.25 (3H, d); 1.5 (2H, m); 1.7 (1H, m); 1.85 (3H, t); 1.9 (1H, m); 1.95 (3H, t); 2.15 (2H, t); 2.2 (2H, t); 2.6 (1H, m); 3.7 (3H, s); 4.9 (1H, m); 5.95 (1H, s); 6.15 (1H, d); 6.4 (1H, m); 7.0 (1H, d).

Example 6

Modified Curtius Rearrangement

Compound **17a** (35 mg, 0.09 mmol), diphenylphosphoryl azide (124 mg, 0.45 mmol) and Et_3N (63 μL, 0.45 mmol) was dissolved in C_6H_6 (8.0 mL) and refluxed for 9.0 h. The reaction mixture was cooled to RT, and anhydrous MeOH (2.0 mL) was added. The reaction was warmed to reflux for 6.0 h, then the reaction mixture was concentrated directly *in vacuo*. The remaining organic residue was flash chromatographed (30% EtOAc in hexanes eluant) to provide (±)myxopyronin A (26.6 mg, 71% yield) as a yellow oil. ^1H NMR (300 MHz, $CDCl_3$): δ 7.0 (d, *J* = 11.6 Hz, 1H); 6.47 (m, 1H); 6.23 (m, 1H); 6.16 (d, *J* = 11.5 Hz, 1H); 5.94 (s, 1H); 4.94 (m, 1H); 3.72 (s, 3H); 2.6 (m, 1H); 2.15 (t, *J* = 7.7 Hz, 2H); 2.05 (m, 2H); 2.01 (s, 3H); 1.85 (s, 3H); 1.76 (m, 1H); 1.57 (m, 1H); 1.51 (m, 1H); 1.25 (d, *J* = 6.8 Hz, 3H); 0.92 (t, *J* = 7.3 Hz, 3H). ^1H NMR (300 MHz, CD_3OD): δ 7.15 (d, *J* = 12.0 Hz, 1H); 6.39 (d, *J* = 14.2 Hz, 1H); 6.27 (d, J = 12.0 Hz, 1H); 6.10 (s, 1H); 5.03 (dt, *J* = 7.1, 14.0 Hz, 1H); 3.66 (s, 3H); 2.68 (m, 1H); 2.19 (t, *J* = 7.4 Hz, 2H); 2.01 (m, 2H); 1.93 (s, 3H); 1.81 (s, 3H); 1.76 (m, 1H); 1.59 (m, 1H); 1.52 (m, 2H); 1.25 (d, *J* = 6.9 Hz, 3H); 0.92 (t, *J* = 7.2 Hz, 3H). MS (FABMS): (M+H) calc. 418, anal. 418. IR (Film, KBr): ν_{max} = 3318 m (b), 2966 s, 2931 s, 2872 m, 1736 s, 1719 s, 1684 m, 1637 s, 1560 s, 1542 s, 1525 s, 1437 m, 1378 m, 1237 m, 1049 m. UV (methanol): λ_{max} (log ε): 224 nm (4.17), 295 nm (4.04).

Saponification of pyrone ester 17

To a round-bottomed flask containing 25.8 mg (62 μmol, 1 equiv) of the pyrone ester **17** dissolved in 5 mL of 2:2:1 methanol/THF/H_2O was added 26 mg (620 μmol, 10 equiv) of $LiOH \cdot H_2O$. The solution is stirred at RT for 24 h. The reaction was quenched by the addition of 1% HCl solution. The aqueous solution is extracted with ethyl acetate (3 x 10 mL). The combined organic layers are dried with Na_2SO_4, filtered and evaporated *in vacuo* to provide 25 mg of an oily yellow residue. The residue (compound **17a**) was isolated used in the next step without any further purification. Since it was crude, compound **17a** was not fully characterized. ^1H NMR (400 MHz, $CDCl_3$): δ 7.03 (dt, J = 6.9, 15.7 Hz, 1H); 7.00 (d, J = 11.7 Hz, 1H); 6.16 (d, J = 11.6 Hz, 1H); 5.96 (s, 1H); 5.85 (d, J = 15.7 Hz, 1H); 2.61 (m, 1H); 2.25 (m, 2H); 2.15 (t, J = 7.6 Hz, 2H); 2.00 (s, 3H); 1.91 (m, 1H); 1.85 (s, 3H); 1.69 (m, 1H); 1.49 (m, 2H); 1.27 (d, J = 6.9 Hz, 3H); 0.91 (t, J = 7.3 Hz, 3H). MS (FABMS): (M+H) calc. 389, anal. 389. IR (Film, KBr): ν_{max} = 3436 m (b), 2966 s, 2931 s, 2872 m, 1731 s, 1713 s, 1613 s, 1548 s (b), 1443 m, 1384 m, 1255 m.

Preparation of allyl alcohol **14**

To a solution of freshly distilled $COCl_2$ (480 μL, 5.5 mmol) in CH_2Cl_2 (15 mL) was added DMSO (850 μL, 12 mmol) at -78 °C. The reaction mixture was stirred at -78 °C for 30 min, then the starting alcohol **13a** (570 mg, 5.0 mmol, dissolved in 3.0 mL CH_2Cl_2, plus 2.0 mL wash) was added. This whole reaction mixture was stirred at -78 °C for another 30 min then Et_3N

(3.5 mL, 25 mmol) was added. The reaction was stirred for 1.0 h at -78 °C, then warmed to RT for 1.0 h before being quenched by H_2O. The reaction mixture was extracted with CH_2Cl_2 (2 x 80 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to afford the crude aldehyde. The crude product was purified by flash chromatography (10% EtOAc in hexanes eluant) to provide viscous aldehyde **14** (548 mg, 98% yield) as a colorless oil. ^1H NMR (400 MHz, $CDCl_3$): δ 0.91 (t, 3H); 1.51 (m, 2H); 2.14 (s, 3H); 2.2 (t, 2H); 5.9 (d, 1H); 10.0 (d, 1H). ^{13}C NMR (67.5 MHz, $CDCl_3$): δ 14.01; 17.81; 20.69; 42.96; 127.75; 164.49; 191.67.

Preparation of pyrone **5**

To a flame-dried flask under a fluching argon atmosphere containing carboxylic acid **4a** (10.55 gm, 91 mmol, 1 equiv dissolved in 250 mL of freshly distilled THF) was added carbonyldiimidazole (16.22 gm, 100 mmol, 1.1 equiv). The reaction was left stirring for 12 h before being concentrated via a rotary evaporator. The residue was partitioned between 100 mL of $CHCl_3$ and 100 mL of 10% HCl. The aqueous layer was extracted with $CHCl_3$ (2 x 50 mL). The combined organic layers were dried with Na_2SO_4, filtered and evaporated on a rotary evaporator. The product needed no further purification as long as it was left on a vacuum pump for sufficient duration in order to remove any remaining starting acid. This yielded compound **5** (8.8 gm, 98%) as a tan solid. ^1H NMR (300 MHz, $CDCl_3$): δ 5.91 (s, 1H); 3.10 (q, J = 7.3 Hz, 2H); 2.53 (q, J = 7.2 Hz, 2H); 1.24 (t, J = 7.5 Hz, 3H); 1.15 (t, J = 7.2 Hz, 3H). ^{13}C NMR (75 MHz,

$CDCl_3$): δ 208.36; 181.16; 173.52; 161.16; 99.92; 99.56; 35.372; 27.52; 10.49; 7.78. MS (EI): calc. 196.0, anal. 196.0. IR (Film, KBr): ν_{max} = 3400 m (b), 3020 s, 1710 s (b), 1625 m (b), 1555 s (b), 1430 w (b), 1315 vs, 760 vs (b).

Preparation iodide **8b**

To a solution of imidazole (10.2 gm, 150 mmol) and triphenylphosphine (14.4 gm, 55 mmol) in CH_2Cl_2 (200 mL) at 0°C was added I_2 (14.0 gm, 55 mmol). After 10 min, a solution of alcohol **8a** (9.5 gm, 50 mmol) in CH_2Cl_2 (100 mL) was added over 5 min. The mixture was warmed to RT, covered in aluminum foil, and stirred for an additional 15 h in the dark. The reaction was then diluted with 2.0 mL saturated $Na_2S_2O_4$ aqueous solution before further dilution with water (150 mL). The organic layer was separated and the aqueous layer was back extracted with CH_2Cl_2 (2x80 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The crude product was purified by flash chromatography (2% EtOAc in hexanes eluant) to afford iodide **8b** (14.4 gm, 96% yield) as a pale oil. ^1H NMR (400 MHz, $CDCl_3$): δ 3.64 (t, 2H); 3.25 (t, 2H); 1.96 (m, 2H); 0.87 (s, 9H); 0.05 (s, 6H). ^{13}C NMR (67.5 MHz, $CDCl_3$): δ 62.32; 36.14; 25.90; 8.26; 3.61; -5.33.

Preparation of allyl alcohol **13a**

To a white slurry solution of zirconocene dichloride (11.7 gm, 40 mmol) in 100 mL $(CH_2)_2Cl_2$ was added $AlMe_3$ (40 mL, 2.0 **M** in hexanes, 80 mmol) at 0°C, stirred for 45 min, and then

warmed to RT for 1.5 h. To this lemon-yellow solution was added 1-pentyne (2.72 gm, 40 mmol, dissolved in 20 mL $(CH_2)_2Cl_2$) at RT. The reaction was allowed to stir for 3.0 h. Then the solvent and the unreacted trimethylalane were evaporated under reduced pressure (maximum 50°C, 0.3 mm Hg, 2~3 h). The remaining orange-yellow organic residue was extracted with dry hexanes (4 x 30 mL), and the yellow extract was transferred to a 500 mL round-bottom flask via a cannula. To this was added ^{n}BuLi (16 mL, 2.5 M in hexanes, 40 mmol) at 0°C. This orange-yellow slurry solution was stirred from 0°C to RT for 1.5 h, and then THF (70 mL) was added to dissolve the precipitate. The resulting solution (homogeneous, brown-yellow color) was cannulated to a suspension of paraformaldehyde in THF under a N_2 atmosphere. This orange-yellow suspension solution was allowed to stir at RT for 20 min.

The reaction was cooled to 0°C (ice water bath), ice was added to quench the reaction, and then saturated NH_4Cl (100 mL) was added. The ice bath was removed and the reaction was further acidified with 3 M HCl until the reaction turned to a clear yellow (homogeneous) solution. At this time, the reaction pH was 2~3. The organic layer was separated, and the aqueous layer was extracted with ether (2x150 mL). The organic extracts were combined and washed with a saturated solution $NaHCO_3$ (200 mL), then dried with Na_2SO_4, filtered and concentrated under reduced pressure to provide crude allylic alcohol **13a**. The crude product was purified by flash chromatography (20% EtOAc in hexanes eluant) to afford alcohol **13a** (3.37 gm, 74% yield) as a

colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.4 (t, 1H); 4.1 (d, 2H); 1.9 (t, 2H); 1.65 (s, 3H); 1.4 (m, 2H); 0.85 (t, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 139.15; 123.33; 59.01; 58.97; 41.54; 41.50; 20.61; 15.88; 13.57.

Preparation of acid **4a**

Ethyl propionate (25 gm, 175 mmol) was dissolved in 30 mL of 1.5 M solution NaOH and stirred at RT for 38 h. The reaction was cooled to 0°C, and 3 M HCl was slowly added until the reaction system reached a pH ~1, then solid KCl was added to saturate the reaction, followed by EtOAc extraction (3x100 mL), and $CHCl_3$ (2x100 mL). The combined organic layers were dried with Na_2SO_4, filtered and evaporated on a rotary evaporator. This protocol afforded the carboxylic acid **4a** (15.5 gm, 76% yield) as a white solid. The product needed no further purification and was used directly in the next step. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.52 (s, 2H); 2.60 (q, J = 7.3 Hz, 2H); 1.10 (t, J = 7.3 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 204.28; 172.32; 47.87; 36.60; 7.45. MS (EI): calc. 116.1, anal. 116.1. IR (Film, KBr): ν_{max} = 3400 m (b), 3020 s, 1708 s (b), 1620 w, 1410 m, 1300 m, 1218 vs, 1110 w, 1040 w, 925 w, 760 vs.

Preparation of alcohol **8a**

To a suspension of NaH (4.0 gm, 100 mmol, 60% dispension in mineral oil) in THF (100 mL) at RT was added 1,3-propane diol (7.6 gm, 100 mmol, dissolved in 50 mL of THF) via a cannula. The resulting mixture was stirred at RT for 45 min, then a solution of TBSCl (15.0 gm, 100 mmol) in 50 mL

THF was added into the reaction mixture by a cannula. This resulting reaction mixture was stirred for 1.0 h at RT. The reaction was quenched with saturated $NaHCO_3$ aqueous solution (200 mL), and extracted with ether (2 x 200 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The crude product was purified by flash chromatography (20% EtOAc in petroleum ether eluant) to afford the pure mono-protected alcohol **8a** (18.1 gm, 98% yield) as a clear oil. ^1H NMR (400 MHz, $CDCl_3$): δ 3.73-3.80 (m, 4H); 2.71 (br s, 1H); 1.74 (m, 2H); 0.86 (s, 9H); 0.04 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 62.70; 62.16; 34.22; 25.89; 25.81; 25.76; 18.13; -5.55.

Preparation of pyrone **5a**

To a stirred solution of diisopropylamine (3.34 mL, 24 mmol) in 25 mL THF at -78°C under an argon atmosphere was added n-butyl lithium (9.45 mL, 2.5 M solution in hexanes, 23.6 mmol). The mixture was allowed to warm to 0°C for 30 min and then recooled to -78°C. The resulting solution was treated with a solution of pyrone **5** (1.47 gm, 7.5 mmol) in 10 mL of THF, and stirred for 1.0 h at -78°C. The derived dianion was treated with iodide **8b** (2.5 gm, 8.25 mmol) in 10 mL THF, followed by the addition of HMPA (4.0 mL, 23.2 mmol). The reaction mixture was allowed to stir for 30 min at -78 °C, before being diluted with saturated NH_4Cl aqueous solution (50 mL). The organic layer was separated, and the aqueous layer was extracted with ether (2 x 50 mL). All organic layers were combined and dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The resulting crude oil was

purified by flash chromatography (20% EtOAc in hexanes eluant) to afford the pure alkylation product **5a** (2.4 gm, 87% yield) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.90 (s, 1H); 3.57 (t, 2H); 3.08 (q, 2H); 2.56 (m, 1H); 1.43-1.73 (m, 3H); 1.22 (d, J = 7.3 Hz, 3H); 1.13 (t, 3H); 0.86 (s, 9H); 0.01 (s, 6H). ^{13}C NMR (67.5 MHz, $CDCl_3$): δ 207.81; 180.57; 175.56; 160.64; 99.28; 62.16; 38.27; 34.81; 29.99; 29.72; 25.44; 17.82; 17.48; 7.27; -5.82.

Preparation of diol **5b**

A solution of TBS ether **5a** (1.66 gm, 4.5 mmol) in 50 mL of AcOH, THF, and water (3:1:1) was stirred at RT for 15 h. The reaction was diluted with 50 mL water, extracted with $CHCl_3$ (2x100 mL). The combined organic layers were washed with a $NaHCO_3$ saturated solution (1x200 mL). The organic layer was separated, and the aqueous layer was back extracted with $CHCl_3$ (1x100 mL). All combined organic layers were dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The crude product was purified by flash chromatography (40% EtOAc in hexanes eluant) to afford diol **5b** (1.04 gm, 91% yield) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.90 (s, 1H); 3.63 (br s, 1H); 3.08 (q, 2H); 2.58 (m, 1H); 1.71-1.80 (m, 1H); 1.50-1.62 (m, 3H); 1.33 (br s, 1H); 1.23 (d, J = 7.33 Hz, 3H); 1.13 (t, 3H). ^{13}C NMR (67.5 MHz, $CDCl_3$): δ 180.45; 175.20; 160.62; 99.30; 99.03; 61.62; 38.14; 34.71; 29.83; 29.46; 17.32; 7.14; 1.51.

Preparation of aldehyde **5c**

To a solution of alcohol **5b** (483 mg, 1.9 mmol) in CH_2Cl_2 (20

mL) was added pyridine (845 μL, 10.45 mmol), followed with Dess-Martin periodinate reagent (2.8 mg, 6.65 mmol) in one portion. The resulting reaction mixture was stirred at RT for 2.0 h before being quenched with saturated $NaHCO_3$ aqueous solution. The reaction mixture was extracted with CH_2Cl_2 (2x60 mL), dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The crude product was flash chromatographed (15% EtOAc in hexanes eluant) to afford aldehyde **5c** (417 mg, 87% yield) as yellow oil. ^1H NMR (400 MHz, $CDCl_3$): δ 5.90 (s, 1H); 3.07 (q, 2H); 2.59 (m, 1H); 2.46 (t, 2H); 1.83-2.02 (m, 2H); 1.23 (d, J = 7.33 Hz, 3H); 1.12 (t, 3H). ^{13}C NMR (67.5 MHz, $CDCl_3$): δ 200.73; 180.69; 174.35; 160.62; 99.93; 99.45; 40.82; 37.82; 35.00; 25.87; 17.52; 7.43; 1.81.

Preparation of acyl pyrone ester **15**

To a solution of triethyl phosphonoacetate (1.4 gm, 6.24 mmol) in C_6H_6 (20 mL) at room temperature was added NaH (210 mg, 5.2 mmol, 60% dispension in mineral oil). The resulting reaction was stirred at RT for 15 min, before aldehyde **5c** (525 mg, 2.08 mmol) in 15 mL C_6H_6 was added, via cannula. The reaction was allowed to stir at RT for 1.0 h before being diluted with aqueous NH_4Cl solution (50 mL). The mixture was extracted with EtOAc (2x100 mL), dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The crude product was flash chromatographed (15% EtOAc in hexanes eluant) to afford compound **15** (596 mg, 89% yield) as a yellow oil. ^1H NMR (400 MHz, $CDCl_3$): δ 6.89 (dt, J = 6.8, 15.6 Hz, 1H); 5.93 (s, 1H); 5.82 (d, J = 15.6 Hz, 1H); 4.17 (q, J = 7.1

Hz, 2H); 3.11 (q, J = 7.1 Hz, 2H); 2.60 (m, 1H); 2.21 (ddd, J = 7.2, 7.3, 7.4 Hz, 2H); 1.89 (m, 1H); 1.69 (m, 1H); 1.28 (t, J = 7.1 Hz, 3H); 1.25 (d, J = 6.9 Hz, 3H); 1.16 (t, J = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 208.38; 180.98; 174.93; 166.37; 161.00; 147.16; 122.38; 100.17; 99.78; 60.37; 38.36; 35.40; 32.32; 29.59; 17.86; 14.29; 7.77. IR (film, KBr): ν_{max} = 2978 s, 2942 s, 1731 s (b), 1637 s, 1631 s, 1554 s, 1443 s, 1272 m, 1178 m, 1043 m.

Preparation of pyrone diol **14a**

Compound **15** (55 mg, 0.17 mmol) was dissolved in 3.5 mL CH_2Cl_2 and stirred at -78°C under argon atmosphere. To this yellow homogeneous solution was added freshly distilled $TiCl_4$ (75 μl, 0.68 mmol), the reaction turned to an orange-yellow slurry mixture instantly. After stirring for 30 min at -78 °C, Et_3N (104 μL, 0.75 mmol) was added, and the reaction became a red-dark reaction mixture. This reaction mixture was allowed to stir at -78°C for 3.0 h, then aldehyde **14** (57 mg, 0.51 mmol) dissolved in 2.0 mL CH_2Cl_2 was added via a cannula. This red-dark reaction mixture was stirred at -78°C for 17 h before it was quenched with distilled water. The reaction was extracted with $CHCl_3$ (3x30 mL), dried (Na_2SO_4), and concentrated *in vacuo*. The crude product was flash chromatographed (25% EtOAc in hexanes eluant) to provide diol **14a** (53 mg, 71% yield) as a sticky yellow oil. ^1H NMR (400 MHz, $CDCl_3$): δ 6.86 (dt, 1H); 5.90 (s, 1H); 5.80 (d, J = 15.87 Hz, 1H); 5.21 (d, J = 8.55 Hz, 1H); 4.74 (m, 1H); 4.08-1.18 (m, 3H); 2.57 (m, 1H); 2.42 (br s, 1H); 2.19

(dt, 2H); 1.94 (t, 2H); 1.83-1.90 (m, 1H); 1.65 (s, 3H); 1.60-1.70 (m, 1H); 1.30-1.43 (m, 2H); 1.19-1.27 (m, 9H); 0.82 (t, 3H).

Preparation of pyrone ester **17**

A stirred solution of diol **14a** (52 mg, 0.12 mmol) in 4 mL CH_2Cl_2 was cooled to -15°C. To this solution was added Et_3N (67 μL, 0.48 mmol), followed by MsCl (28 μL, 0.36 mmol). The yellow solution was stirred at -15°C for 30 min, and then warmed to 0°C for 15 h. To this was added DBU (108 μL, 0.72 mmol), the resulting reaction mixture was stirred from 0°C to RT over a 12 h time period before being diluted with 2% HCl aqueous solution (10 mL). The mixture was stirred for 5 min then extracted with EtOAc (2x15 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo*. The crude product was flash chromatographed (20% EtOAc in hexanes eluant) to provide compound **17** (36 mg, 72% yield) as yellow oil. ^1H NMR (400 MHz, $CDCl_3$): δ 7.00 (d, J = 11.6 Hz, 1H); 6.91 (dt, J = 6.8, 15.6 Hz, 1H); 6.16 (d, J = 11.6 Hz, 1H); 5.95 (s, 1H); 5.83 (d, J = 15.6 Hz, 1H); 4.19 (q, J = 7.1 Hz, 2H); 2.61 (m, 1H); 2.24 (m, 2H); 2.15 (t, J = 7.6 Hz, 2H); 1.91 (m, 1H); 2.01 (s, 3H); 1.85 (s, 3H); 1.69 (m, 1H); 1.49 (m, 2H); 1.29 (t, J = 7.1 Hz, 3 H); 1.27 (d, J = 6.9 Hz, 3H); 0.91 (t, J = 7.3 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 201.72; 180.83; 174.82; 166.42; 160.39; 149.17; 147.25; 133.65; 133.04; 122.37; 120.67; 100.06; 99.17; 60.38; 42.93; 38.27; 32.25; 29.62; 21.04; 17.81; 17.30; 14.29; 13.88; 13.55. MS (FABMS): (M+H) calc. 417, anal. 417. IR (Film, KBr): ν_{max} = 2966 m, 2931 m, 2872 m, 1748 s, 1736 s, 1719 s,

1701 s, 1560 s, 1542 s, 1454 s.

Discussion

The total synthesis of myxopyronin A was approached in several ways. The first is shown in the retrosynthesis provided in Figure 2.

Attachment of the 3-position side chain was accomplished through an aldol condensation. Ester **1** is available from 2-pentanone through Wadsworth-Emmons chemistry (Wadsworth, W., Emmons, W., *Org. Synth.*, **1965**, *45*, 44) and commercially available triethylphosphonates (Figure 3). The anion of triethyl phosphonacetate is created by stirring with NaH in THF, and is condensed with 2-pentanone to create unsaturated ester **16**. The ester **16** is reduced with DIBAL to the alcohol and then oxidized to the aldehyde **14** with DDQ. Compound **1** is produced by going through another cycle of Wadsworth-Emmons chemistry, DIBAL reduction and DDQ oxidation. Intermediate **13** can also be made using lithium dimethyl cuprate chemistry (Sum and Weiler, *Can. J. Chem.*, **1979**, *57*, 1431), which procedure produces **13** in a higher E/Z ratio.

The other half of the molecule containing the 6-substituted pyrone is dissected in the following manner. This scheme requires a pyrone functionalized at the 6-position (Douglas, J., Money, T., *Can. J. Chem.*, **1968**, *46*, 695) and commercially available reagents shown in Figure 2. The three necessary segments can be joined by an additional Wadsworth-Emmons olefination and a simple alkylation. The

terminal methyl carbamate can then be introduced by the use of a modified Curtius rearrangement. Overman, L., Taylor, G., Petty, C., Jessup, P., *J. Org. Chem.*, **1978**, *43*, 2164.

Two different pathways are provided for the synthesis of compound **10**. The first pathway is based on the known alkylation of the commercially available compound **3** at the 7-postion using n-BuLi and an alkyl halide. Groutas, W., Stanga, M., Brubaker, M., Huang, T., Moi, M., Carroll, R., *J. Med. Chem.*, **1985**, *28*, 1106. (see Figure 4) A model pyrone containing an ethyl group was alkylated at the 7-position in a similar manner by constructing the 6-position side chain after the desired methyl group (C-8) was already in place at C-7. (The synthetic approach used to synthesize the 6-ethyl pyrone was developed by Cook and co-workers. Cook, L., Ternai, B., Ghosh, P., *J. Med. Chem.*, **1987**, *30*, 1017.) The present invention provides a means of installing alkyl chains of varying sizes at the 6-position by dimerization of various ethyl malonates and subsequent deacylation of the 3-position (Figures 5 and 15). Thereby, pyrone **6** is prepared where R is ethyl.

Pyrone **6** is then alkylated with 3-bromopropionaldehyde dimethyl acetal and the 4-hydroxyl group protected as its SEM ether (Figure 6). The dimethyl acetal is removed with dilute H_2SO_4. The Wadsworth-Emmons reaction (Wadsworth, W., Emmons, W., *Org. Synth.*, **1965**,45,44) introduces the unsaturated ester, and the SEM group is removed with TBAF to produce key intermediate **10**. The 3-position side chain is introduced by use of an aldol reaction. The ester on the 6-position side chain is hydrolyzed, and a Curtius

rearrangement installs a vinyl carbamate moiety to complete the synthesis of myxopyronin A.

In a preferred embodiment, the present invention provides an improved route to intermediate **10**. Allyl bromide alkylates pyrone **6** in a higher yield (Figure 7). This modification combined with the use of dilute H_2SO_4 in place of TBAF to remove the SEM group substantially increases the overall yield of **10**.

Figure 8 schematically demonstrates the completion of the myxopyronin A synthesis from key intermediate **10**. Aldol condensation with **1** to produce **13** is followed by oxidation with any reagent effective for oxidizing alcohols at allylic or benzylic positions, including DDQ, MnO_2, K_2CrO_7, etc., to afford ketone **17**. Conversion of the ethyl ester to the acid is effected by saponification with LiOH. Finally, installation of the vinyl carbamate is effected by modified Curtius conditions.

In addition, the present invention provides an alternate pathway for the total synthesis of myxopyronin A. Formation of the bond between C-3 and C-15 has proven to be a difficult synthetic step. A study of alternative ways of appending the 3-position side chain demonstrated that attachment of a portion of the 3-position alkyl chain is effectively performed by acylation of the pyrone. This process is based on acylation of 6-alkyl-4-hydroxy-2-pyrones by acyl chlorides. Cook, L., Ternai, B., Ghosh, P., *J. Med. Chem.*, **1987**, *30*, 1017. However, acylation of pyrone **10** with acyl chloride **19** using conditions set forth by Cook (Figure 9) did not provide the expected product: no evidence of the

double bonds were observed by NMR; only compound **10** was recovered.

Acylation of pyrones is successful when acid chlorides with saturated alkyl chains are used. A retrosynthetic analysis of the preparation of myxopyronin A taking advantage of this reaction is shown, in Figure 10. Pyrone **10** was synthesized as shown in Figures 5-7. At this point, the pyrone is acylated with propionyl chloride. The rest of the 6-position side chain is then attached using a base-catalyzed aldol reaction with aldehyde **14**, an intermediate in the synthesis of **1** (Figure 3) and the 3-propionyl pyrone **15**. The synthesis is completed with a Curtius rearrangement as illustrated in Figure 8.

The alternate route works effectively as disclosed herein. Pyrone intermediate **10** is acylated with propionyl chloride in TFA to give compound **15**. An aldol reaction using LDA in THF condenses aldehyde **14** with **15**. Subsequent treatment with MsCl and DBU gives the desired diene in the side chain and yields intermediate **17**.

Analogs of Myxopyronins

As will be apparent to one of skill in the art, various isomers (including stereoisomers), analogs, and derivatives of the pyronins are made accessible by the subject invention by appropriate modification. For example, the total synthesis of myxopyronin B is easily carried out by simply substituting 2-hexanone for 2-pentanone at the beginning of the synthesis (Figure 3). As disclosed herein, the synthetic pathways provide a mixture of enantiomers which

can be prepared in purified form by any of a variety of methods well known in the art, including but not limited to chiral HPLC, resolution of one of the intermediates set forth herein, or separation of a diastereomeric derivative.

Convergent Synthesis of Myxopyronin A

Pyrones have been used to elicit a biological effect in a few instances but in none of them have they been used as an antibacterial agent. 2H-pyran-2,6(3H)-dione derivatives are reported to be active at reasonable doses in a passive cutaneous anaphylaxis model in rats when administered by either the intravenous or oral route. Snader, K.M. et al., *J. Med. Chem.*, **1979**, *22*, 706; Chahrin, L.W., Snader, K.M., Williams, C.R., 2H-Pyran-2,6(3H)-dionederivate, German Patent 25 33 843. In a second case, simple 3-(1-oxoalkyl)-4-hydroxy-6-alkyl-2-pyrones were found to be effective *in vitro* in the inhibition of human sputum elastase. Cook, L., Ternai, B., Ghosh, P., *J . Med. Chem.*, **1987**, *30*, 1017. Lastly, a series of coumarin derivatives were found to be effective inhibitors of HIV protease in both enzymatic assays and cell culture (Figure 1(b)). Skulnick, H.I., et al., *J. Med. Chem.*, **1995**, *38*, 4968. No synthetic investigations of pyronin antibacterials have been reported in the literature. The total synthesis of myxopyronin A was approached in a highly convergent manner. The retrosynthesis of myxopyronin A is shown in Figure 11.

Preparation of compound **14** (Figure 12(a)) was started from commercially available 1-pentyne. Regioselective and ster-eospecific carboalumination of 1-pentyne in the

presence of 2.0 equiv of $AlMe_3$ and 1.0 equiv of Cp_2ZrCl_2 (Cp = η-C_5H_5) afforded the organoalane species, which was treated with 1.0 equiv of $^{n-}$BuLi, and quenched with paraformaldehyde to give geometrically pure (E) allylic alcohol **13a** with 74% yield. Swern oxidation of alcohol **13a** cleanly generated versatile aldehyde **14**, which is not very stable and used immediately after flash chromatography.

A synthetic approach to pyrone **5** (R=Et) (Figure 12(b)) was based on a known procedure reported by Cook and co-workers (*supra*). Commercially available ethyl propionyl-acetate was hydrolyzed under basic conditions (1.5 M aqueous NaOH) to provide acid **4a** (76% yield), which was dimerized, in the presence of carbonyldiimidazole, to afford pyrone **5** (R=Et) in 98% yield. This sequence of reactions easily provided a quantitative amount of pyrone **5**(R=Et), which is the core structure in the myxopyronin A structure.

Preparation of compound **8b** (Figure 12(c)) is straight forward. Monoprotection of 1,3-propane diol was achieved by using 1.0 equiv of NaH and 1.0 equiv of TBSCl, and it cleanly generated alcohol **8a** in 98% isolated yield. Iodination of alcohol **8a** under the condition of I_2/PPh_3/imidazole provided iodide **8b** as a single product with 96% yield.

Subsequent research has led to an improved synthetic approach to the intermediate **15** (Figure 13(a)). Pyrone **5** (R=Et) was lithiated (3.2 equiv of LDA) at -78°C, the derived anion was treated with iodide **8b** to afford compound **5a** as a single alkylated product in 80-87% isolated yield. Compound **5a** was deprotonated (AcOH/THF/H_2O, 2:2:1 mixture

solution) at RT to provide alcohol **5b** (91% yield), which was oxidized in the presence of the Dess-Martin periodinate reagent to yield aldehyde **5c**. Wadsworth-Emmons homologation of aldehyde **5c** (triethyl phosphonoacetate, NaH, C_6H_6) cleanly generated α,β-unsaturated ester **15** as a single isomer with a 89% yield. Figure 13(b) schematically demonstrates the completion of the myxopyronin A synthesis from key intermediate **15**.

Aldol condensation of ethyl ketone **15** with aldehyde **14** in the presence of $TiCl_4$ was investigated. Titanium enolate was generated at -78°C by the treatment of ethyl ketone **15** with 4.0 equiv of $TiCl_4$ and 4.4 equiv of Et_3N. The derived (Z)-enolate was condensed with an excess of freshly prepared aldehyde **14** to produce diol **14a** in 71.3% isolated yield. Treatment of diol **14a** with methane sulfonyl chloride, followed by elimination mediated by DBU, furnished the trisubstituted diene **17** in a 72% yield. Conversion of **17** to the α,β-unsaturated acid **17a** was accomplished with LiOH. Finally, installation of the vinyl carbamate functional group was effected through modified Curtius condition. Acid **17a** was combined with diphenylphosphoryl azide ($PhO_2P(O)N_3$) and Et_3N and refluxed in C_6H_6 for 9.0 h. The derived azide intermediate was treated with anhydrous MeOH and was refluxed for another 6.0 h to produce (±)myxopyronin A, compound **18**.

Myxopyronin A Synthesis Aldolization of an Acyl Pyrone

Acylation of pyrones at the 3-position is successful when the acid chlorides of short, saturated alkyl chains are used. Douglas, J., Money, T., *Can. J. Chem.*, **1968**, *46*, 695. Acylation of **10** with propionyl chloride is followed by a base-catalyzed aldol with the appropriate aldehyde to attach the rest of the native side-chain. The necessary aldehyde **14** (Figure 14(a)) is generated by way of the ester **16.** (Sum, F.W., Weiler, L., *Can. J. Chem.*, **1979**, *57*, 431) Reaction of ethyl butyrylacetate with diethyl chlorophosphite and $LiMe_2Cu$ gave predominantly the E, isomer of **16** after distillation. DIBAL reduction to the alcohol followed by Swern oxidation produced the aldehyde **14**.

With aldehyde **14** in hand, the route shown in Figure 14(b) was used to complete the synthesis of myxopyronin A. Pyrone intermediate **10** is acylated with propionyl chloride in TFA to give compound **15**. The overall conversion is efficient since unreacted starting material can be recovered by chromatography. An aldol reaction between the pure regioisomer of **14** and **15** was performed using LDA in THF. The crude alcohol was converted to the mesylate and then eliminated using DBU. This yielded the desired diene **17**.

To complete the synthesis, **17** was saponified to the acid using LiOH. A modified Curtius sequence (Overman, L., Taylor, G., Petty, C., Jessup, P., *J. Org. Chem.*, **1978**, *43*, 2164) was then used to install the unusual vinyl carbamate moiety and thereby afford the desired myxopyronin A. The identity of the product was confirmed by comparison

of spectral data for the synthetic product with that of an authentic sample of the natural product. Resolution of the enantiomers generated at C-7 may be achieved by means of chiral HPLC.

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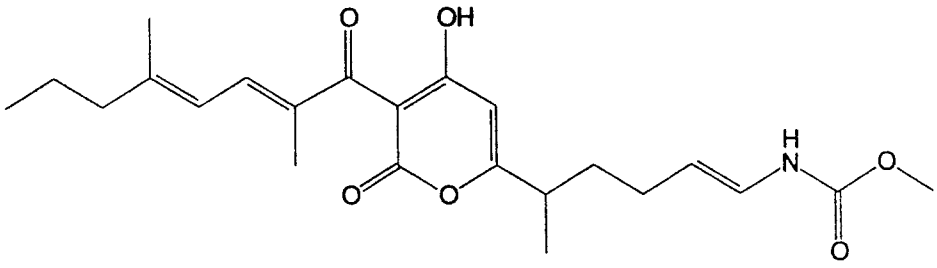
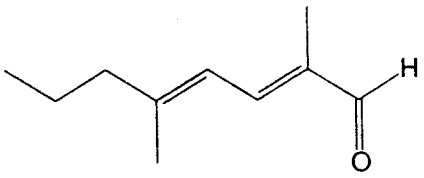
What is claimed is:

1. A process of preparing a myxopyronin having the structure:

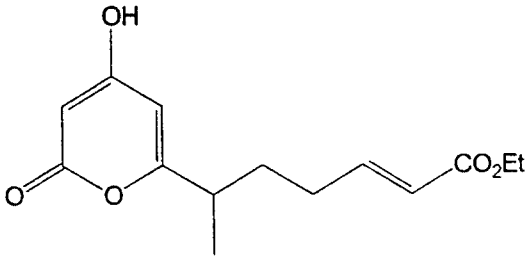


which comprises:

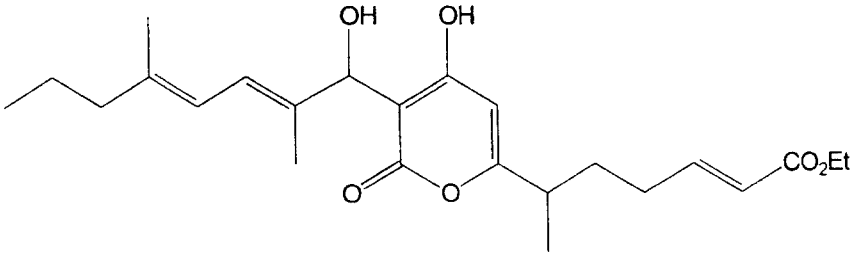
(a) condensing an aldehyde having the structure:



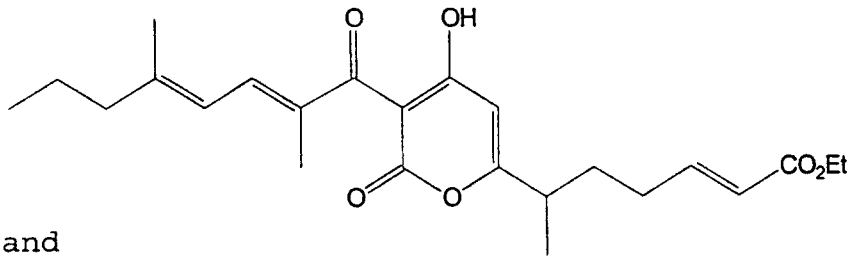
with a pyrone having the structure:



under suitable conditions to form an adduct having the structure:



(b) oxidizing the adduct formed in step (a) under suitable conditions to form a pyrone ketone having the structure:



and

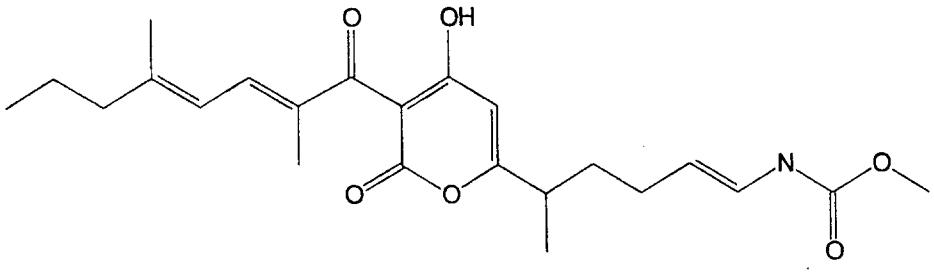
(c) (i) saponifying the pyrone ketone formed in step (b) under suitable conditions to form a pyrone acid;

(ii) acylating the pyrone acid formed in step (c)(i) under suitable conditions to form a pyrone anhydride;

(iii) treating the pyrone anhydride formed in step (c)(ii) with an azide salt to form a pyrone acyl azide; and

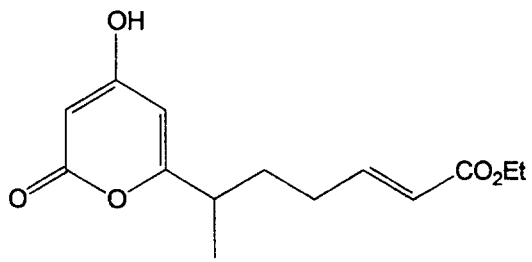
(iv) heating the pyrone acyl azide formed in step (c)(iii) under suitable conditions to form the myxopyronin.

2. A process of preparing a myxopyronin having the structure:

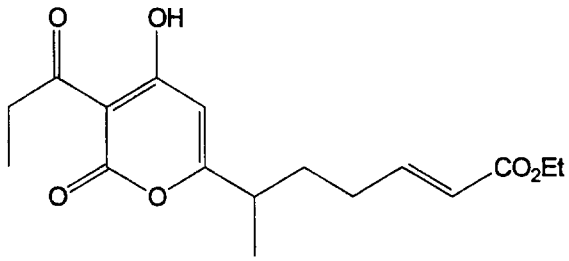


which comprises:

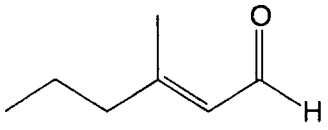
(a) treating a pyrone having the structure:



with propionyl chloride under suitable conditions to form a ketone adduct having the structure:



(b) (i) condensing the ketone adduct formed in step (a) under suitable conditions with an aldehyde having the structure:

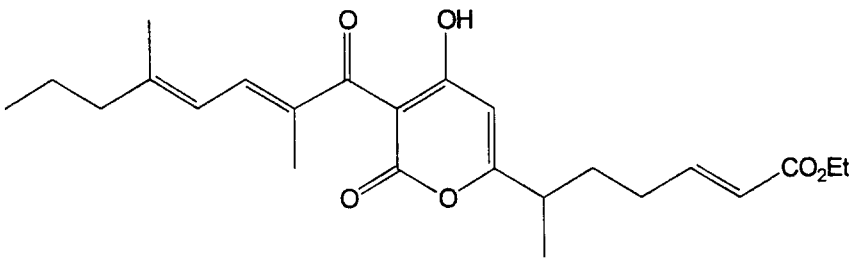


to form a pyrone aldol;

(ii) mesylating the pyrone aldol formed in

step (b)(i) under suitable conditions to form a pyrone aldol mesylate; and

(iii) reacting the pyrone aldol mesylate under suitable basic conditions to form a pyrone ketone having the structure:



and

(c)(i) saponifying the pyrone ketone formed in step (b)(iii) under suitable conditions to form a pyrone acid;

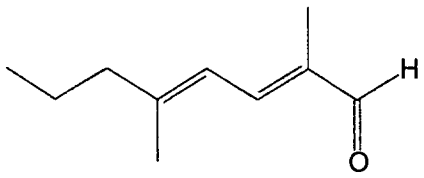
(ii) acylating the pyrone acid formed in step (c)(i) under suitable conditions to form a pyrone anhydride;

(iii) treating the pyrone anhydride formed in step (c)(ii) with an azide salt to form a pyrone acyl azide; and

(iv) heating the pyrone acyl azide formed in step (c)(iii) under

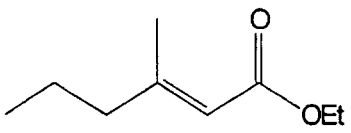
suitable conditions to form the myxopyronin.

3. A process of preparing an unsaturated aldehyde having the structure:



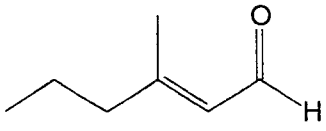
which comprises:

(a) condensing triethyl phosphonacetate with 2-pentanone under suitable conditions to form an unsaturated ester having the structure:



(b) (i) reducing the unsaturated ester formed in step (a) under suitable conditions to form an unsaturated alcohol; and

(ii) oxidizing the unsaturated alcohol under suitable to form an unsaturated aldehyde having the structure:



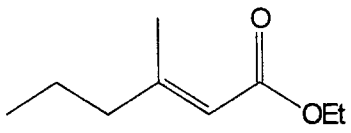
and

(c) (i) condensing triethyl phosphonopropionate with the unsaturated aldehyde formed in step (b)(ii) under suitable conditions to form a diene ester;

(ii) reducing the diene ester formed in step (c)(i) under suitable conditions to form a diene alcohol; and

(ii) oxidizing the unsaturated alcohol under suitable to form the unsaturated aldehyde.

4. The process of claim 3 wherein the unsaturated ester having the structure:



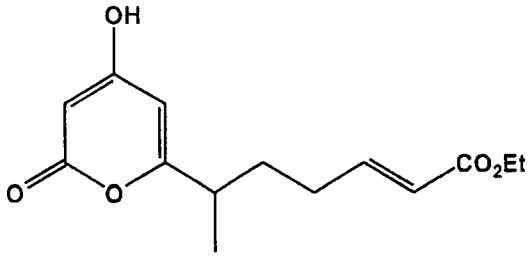
is prepared by

(a) condensing ethyl butyryl acetate with diethyl phosphorochloridate under suitable conditions to form an enol phosphonate; and

(b) alkylating the enol phosphonate formed in

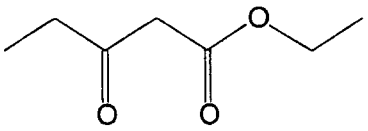
step (a) with an organometallic reagent under suitable conditions to form the unsaturated ester.

5. A process of preparing a pyrone ester having the structure:

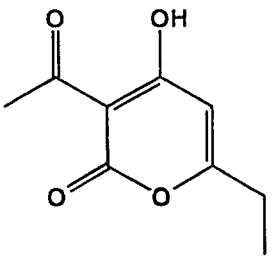


which comprises:

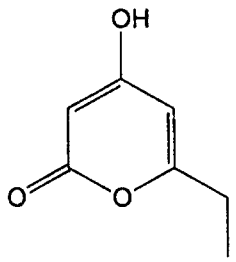
(a) treating a dicarbonyl compound having the structure:



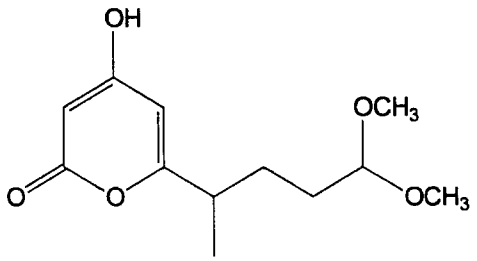
acidifying and dimerizing under suitable conditions to form an acyl pyrone having the structure:



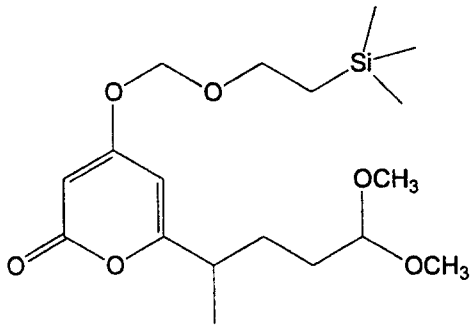
(b) hydrolyzing the acyl pyrone formed in step (a) under suitable conditions to form a pyrone having the structure:



(c) alkylating the pyrone formed in step (b) under suitable conditions to form a pyrone acetal having the structure:

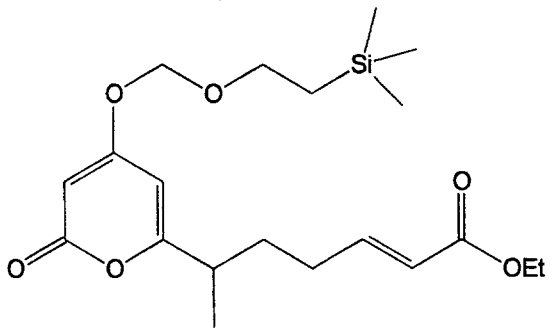


(d) etherifying the pyrone acetal formed in step (c) under suitable conditions to form an ether pyrone acetal having the structure:



(e) (i) acidolytically cleaving the pyrone acetal under suitable conditions to form an aldehyde; and

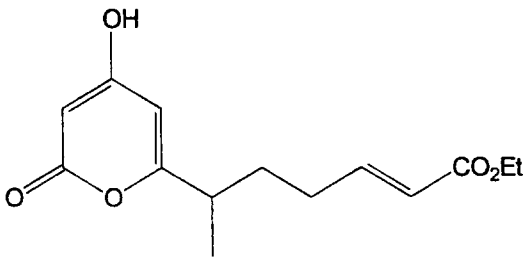
(ii) reacting the aldehyde with triethylphosphonoacetate under suitable conditions to form a protected pyrone ester having the structure:



and

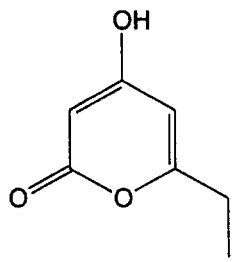
(f) deprotecting the protected pyrone ester under suitable conditions to form the pyrone ester.

6. A process of preparing a pyrone ester having the structure:

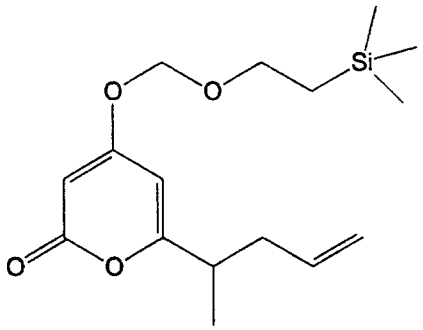


which comprises:

(a) (i) alkylating a pyrone having the structure:

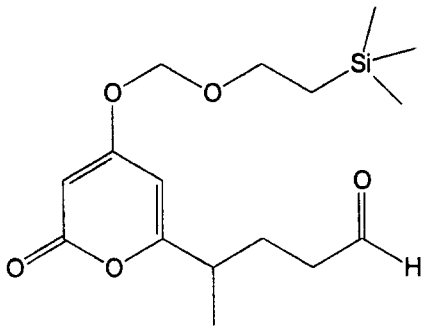


(ii) etherifying the pyrone formed in step (i) under suitable conditions to form protected pyrone having the structure:

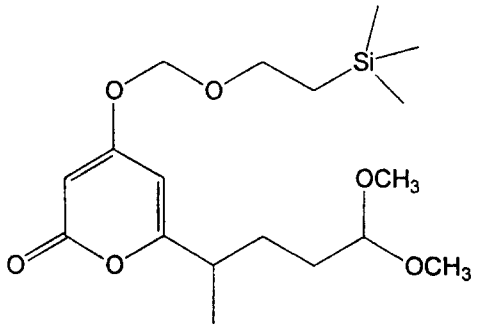


(b) (i) hydroborating the protected pyrone formed in step (a)(ii) under suitable basic conditions; and

(ii) oxidizing under suitable conditions to form a pyrone aldehyde having the structure:



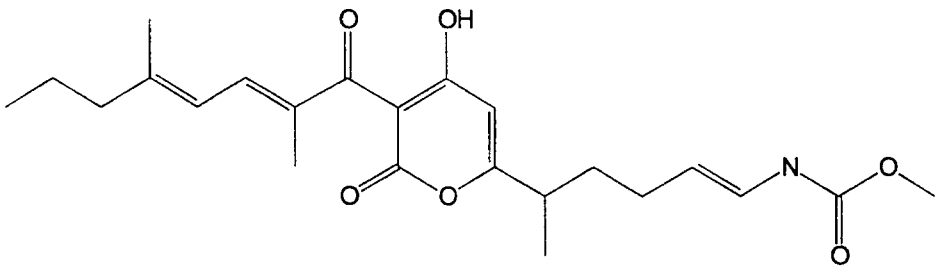
(c) condensing the pyrone aldehyde formed in step (b)(ii) with triethyl phosphonoacetate under suitable conditions to form a protected pyrone ester having the structure:



and

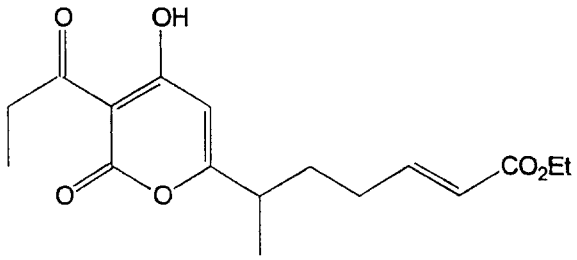
(d) cleaving the protected pyrone ester under suitable conditions to form the pyrone ester.

7. A process of preparing a myxopyronin having the structure:

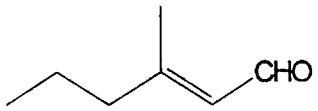


which comprises:

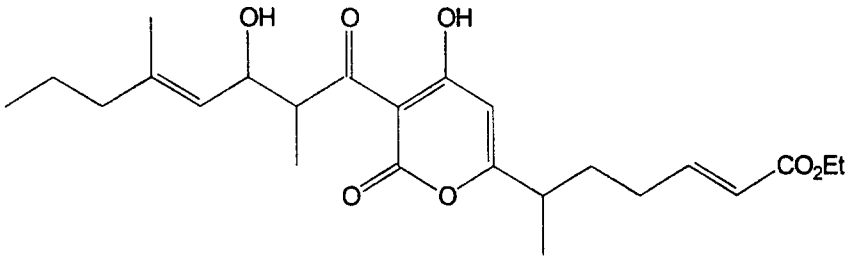
(a) treating an acyl pyrone having the structure:



with an unsaturated aldehyde having the structure:

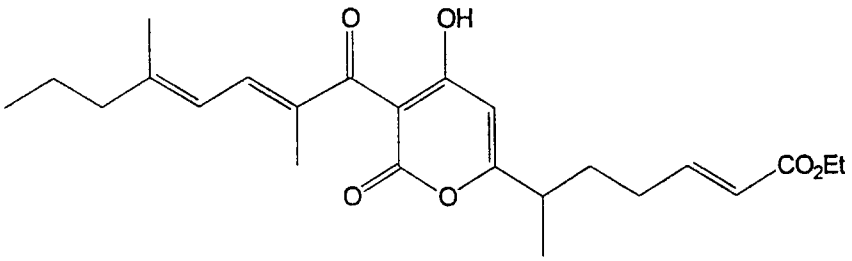


under suitable conditions to form a pyrone aldol having the structure:



(b) (i) mesylating the pyrone aldol formed in step (a) under suitable conditions to form a pyrone aldol mesylate; and

(ii) reacting the pyrone aldol mesylate formed in step (b)(i) under suitable basic conditions to form a pyrone diene having the structure:



and

(c) saponifying the pyrone diene formed in step (b)(ii) under suitable conditions to form a pyrone acid;

(d) converting the pyrone acid formed in step (c) under suitable conditions to a pyrone acyl azide; and

(e) solvolyzing the pyrone acyl azide formed in step (d) with methanol under suitable conditions to form the myxopyronin.

8. The process of claim 7 wherein the acyl pyrone in step (a) is treated with the unsaturated aldehyde in the presence of a Lewis acid catalyst.

9. The process of claim 8 wherein the Lewis acid catalyst is titanium tetrachloride/triethylamine combination.

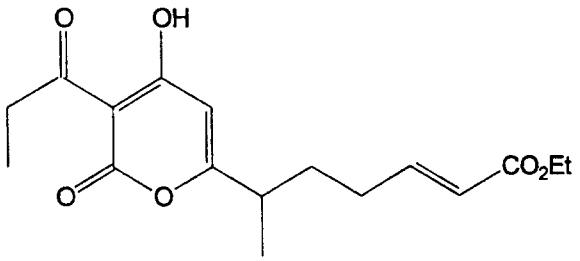
10. The process of claim 7 wherein the pyrone aldol in step (b)(i) is mesylated with mesylchloride in the presence of triethylamine.

11. The process of claim 7 wherein the pyrone aldol mesylate in step (b)(ii) is reacted with DBU.

12. The process of claim 7 wherein the pyrone diene in step (c) is saponified with lithium hydroxide.

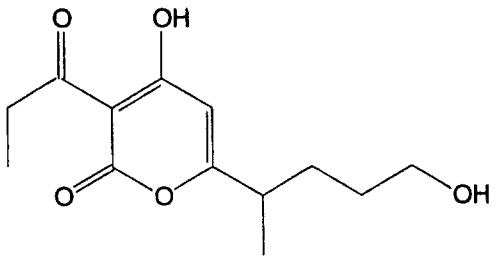
13. The process of claim 7 wherein the pyrone acid in step (d) is converted using diphenylphosphoryl azide in the presence of triethylamine.

14. A process of preparing an acyl pyrone having the structure:

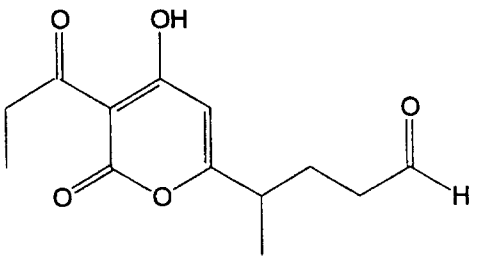


which comprises:

(a) oxidizing a pyrone diol having the structure:



under suitable oxidizing conditions to form a pyrone aldehyde having the structure:



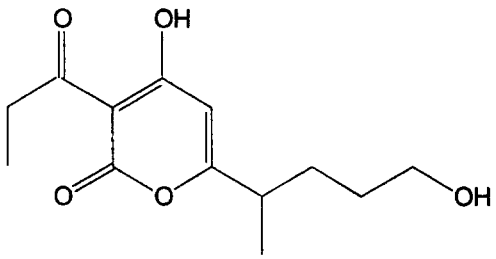
and

(b) condensing the pyrone aldehyde formed in step (a) with triethylphosphonoacetate under suitable basic conditions to form the pyrone ester.

15. The process of claim 14 wherein the pyrone diol in step (a) is oxidized with a Dess-Martin periodinate.

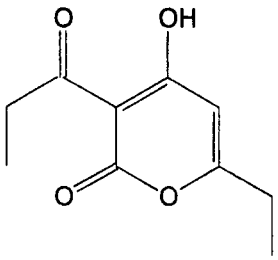
16. The process of claim 14 wherein the condensing step is effected with sodium hydride.

17. A process of preparing a pyrone diol having the structure:



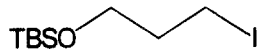
which comprises:

(a) (i) deprotonating an acyl pyrone having the structure:

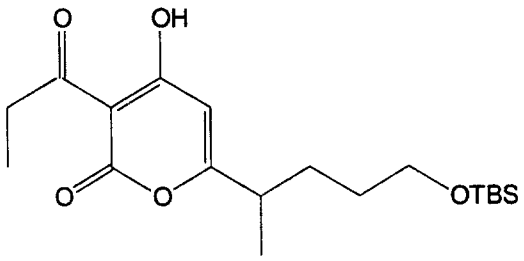


under suitable basic conditions to form an anion; and

(ii) alkylating the anion formed in step (a)(i) with a siloxyalkyl halide having the structure:



under suitable conditions to form an alkylated pyrone having the structure:



and

(b) deprotecting the alkylated pyrone formed in step (a)(ii) under suitable conditions to form the pyrone diol.

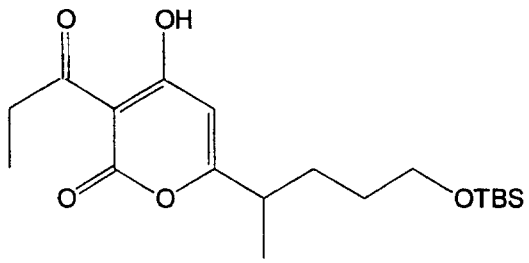
18. The process of claim 17 wherein the acyl pyrone in step (a)(i) is deprotonated using lithium diisopropylamide or lithium diethylamide.

19. The process of claim 17 wherein the alkylated pyrone

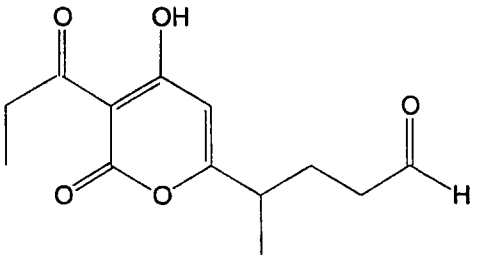
in step (b) is deprotected with a weak acid.

20. The process of claim 19 wherein the weak acid is acetic acid.

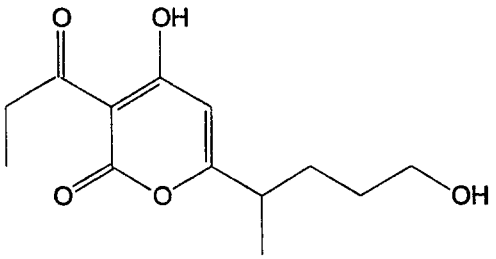
21. A composition of matter having the structure:



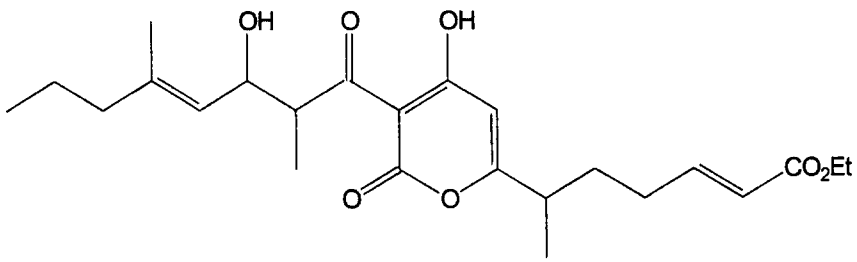
22. A composition of matter having the structure:



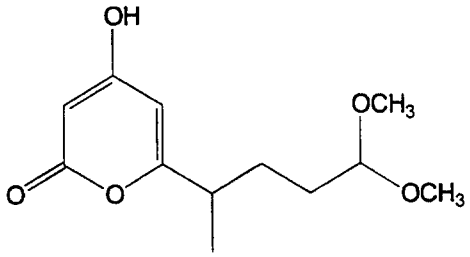
23. A composition of matter having the structure:



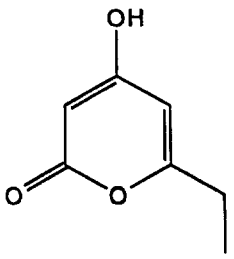
24. A composition of matter having the structure:



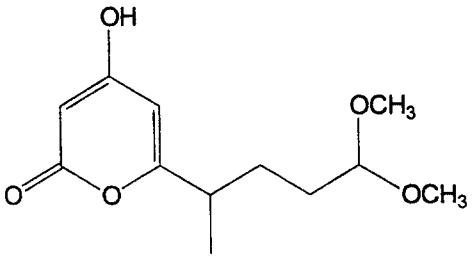
25. A composition of matter having the structure:



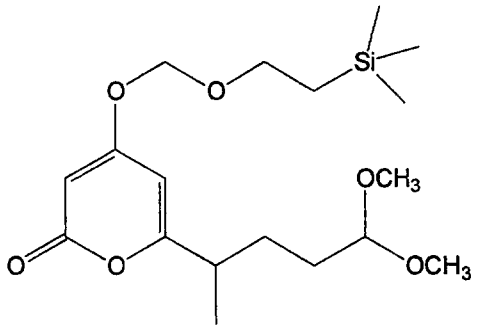
26. A composition of matter having the structure:



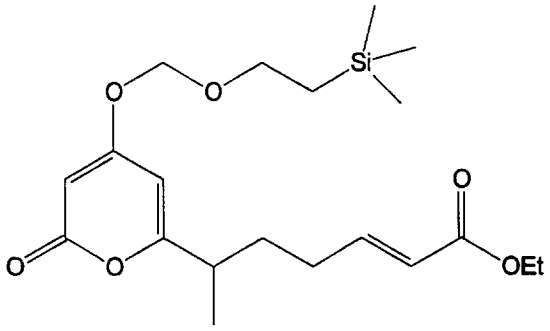
27. A composition of matter having the structure:



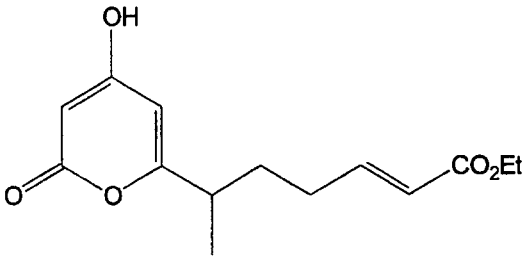
28. A composition of matter having the structure:



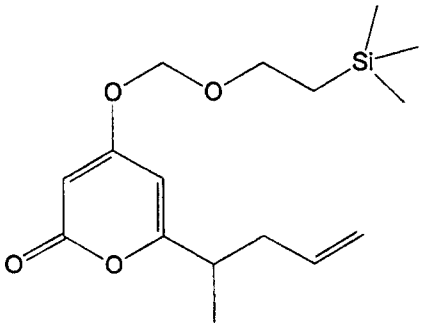
29. A composition of matter having the structure:



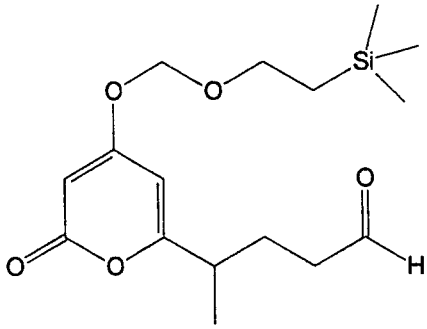
30. A composition of matter having the structure:



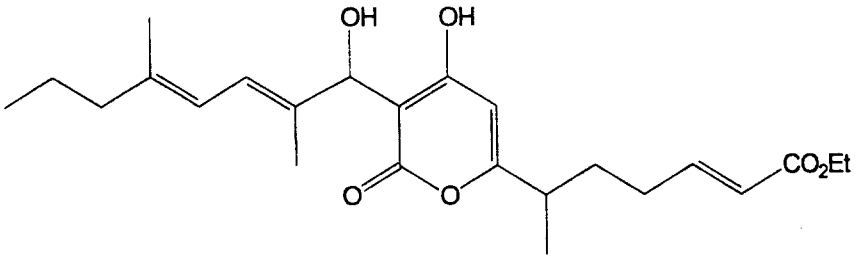
31. A composition of matter having the structure:



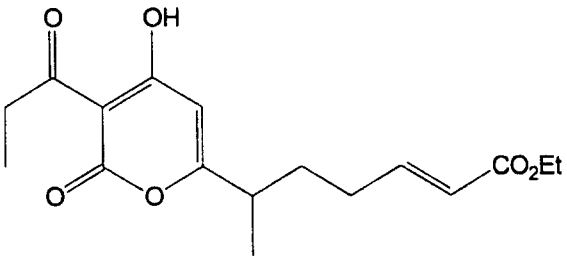
32. A composition of matter having the structure:



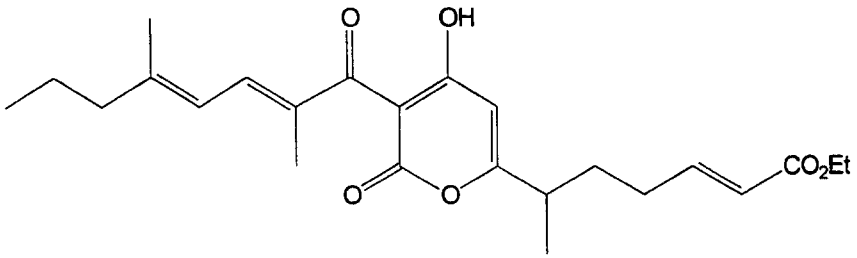
33. A composition of matter having the structure:



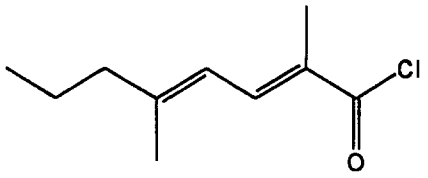
34. A composition of matter having the structure:



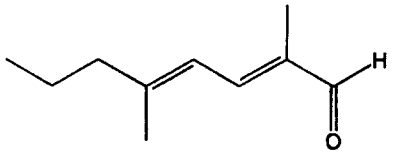
35. A composition of matter having the structure:



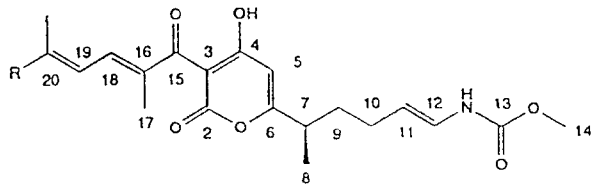
36. A composition of matter having the structure:

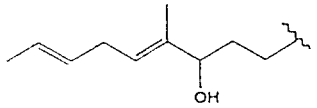


37. A composition of matter having the structure:



1 (a)

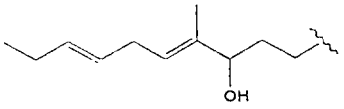




= R : Corallopyronin A

Myxopyronin A : R = n-propyl

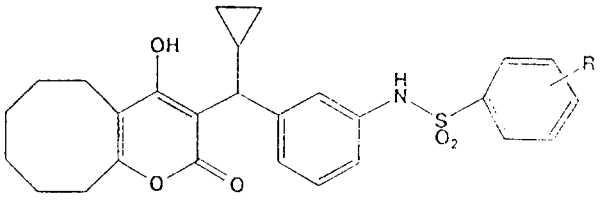
18



= R : Corallopyronin B

Myxopyronin B : R = n-butyl

1 (b)



R= H, CH_3 or CN

FIG. 1

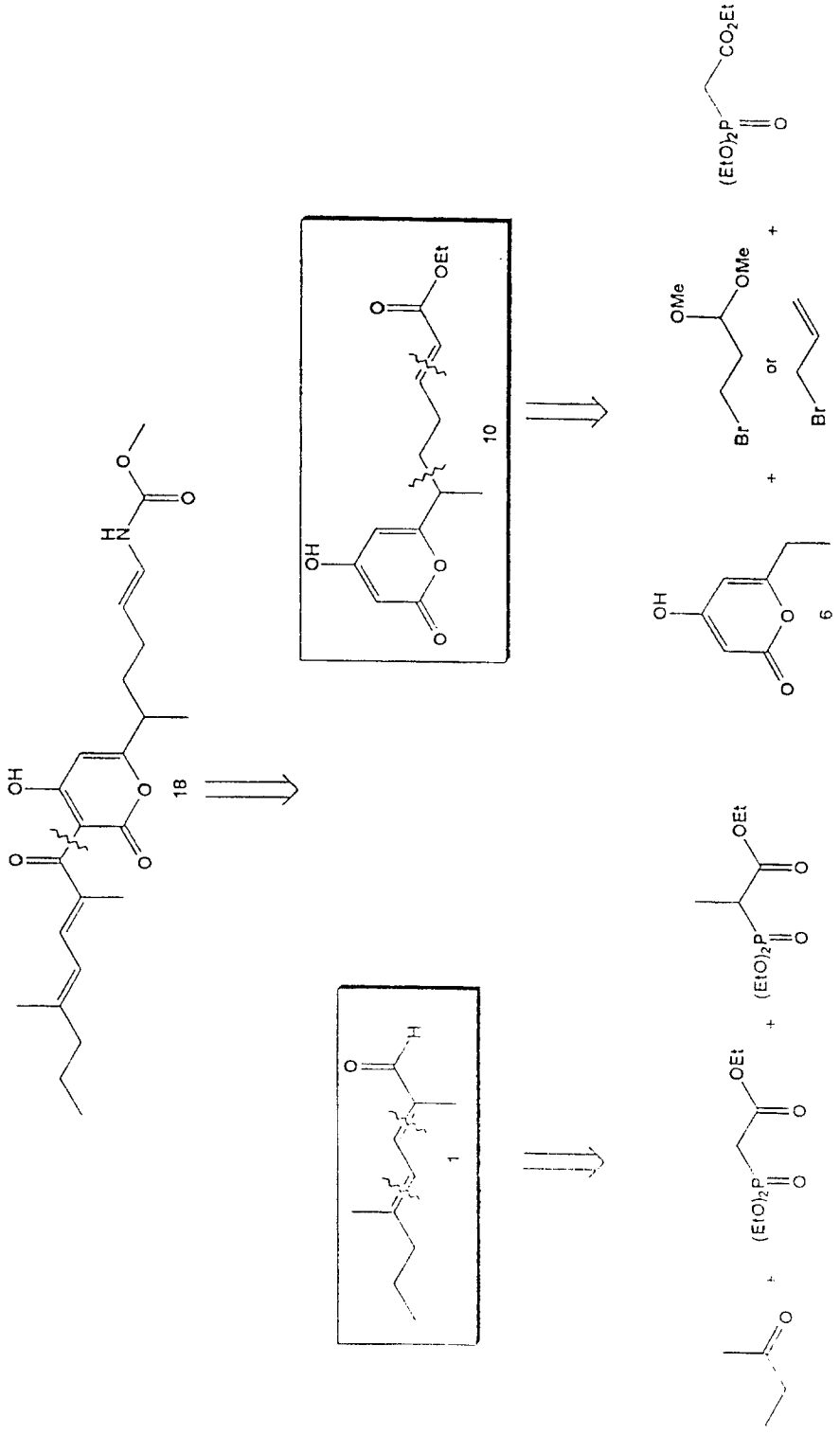


FIG. 2

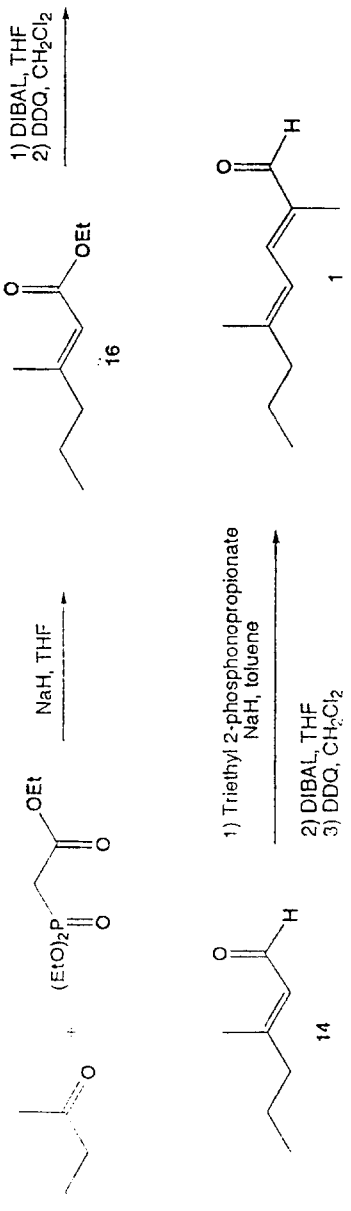

1) DIBAL, THF
2) DDQ, CH_2Cl_2
OEt
O
16
NaH, THF
OEt
O
O
$(EtO)_2P$
O
O
1) Triethyl 2-phosphonopropionate
NaH, toluene
2) DIBAL, THF
3) DDQ, CH_2Cl_2
H
O
14
H
O
1

FIG. 3

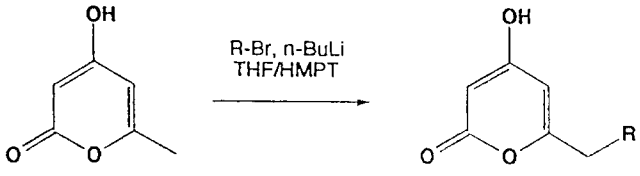


FIG. 4

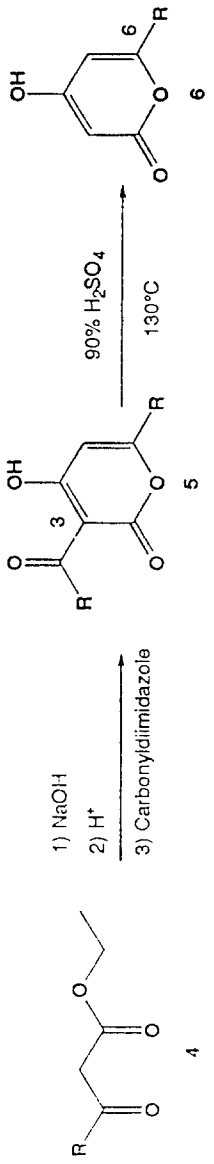


FIG. 5

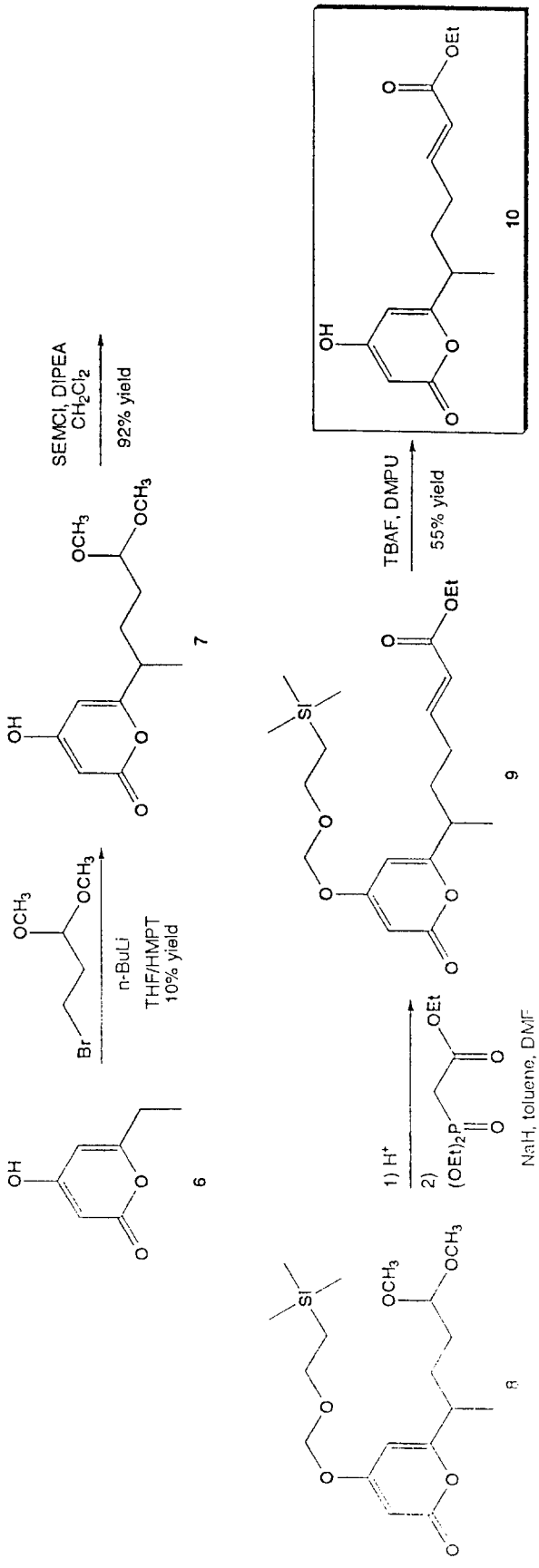

SEMCl, DIPEA
CH_2Cl_2
92% yield
n-BuLi
THF/HMPT
10% yield
1) H^+
2) $(OEt)_2P$
NaH, toluene, DMF
60% yield
TBAF, DMPU
55% yield
6
7
8
9
10

FIG. 6

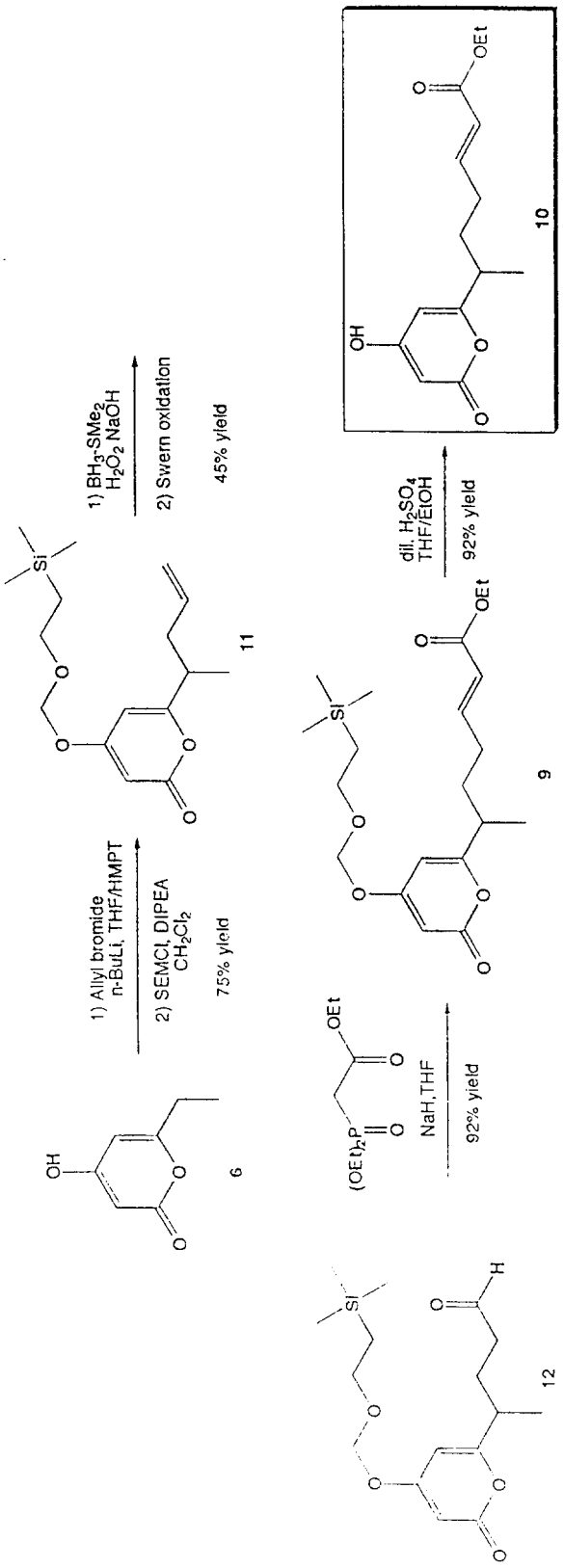

1) Allyl bromide
n-BuLi, THF/HMPT
2) SEMCl, DIPEA
CH_2Cl_2
75% yield
1) BH_3-SMe_2
H_2O_2 NaOH
2) Swern oxidation
45% yield
dil. H_2SO_4
THF/EtOH
92% yield
NaH,THF
92% yield
6
11
9
10
12

FIG. 7

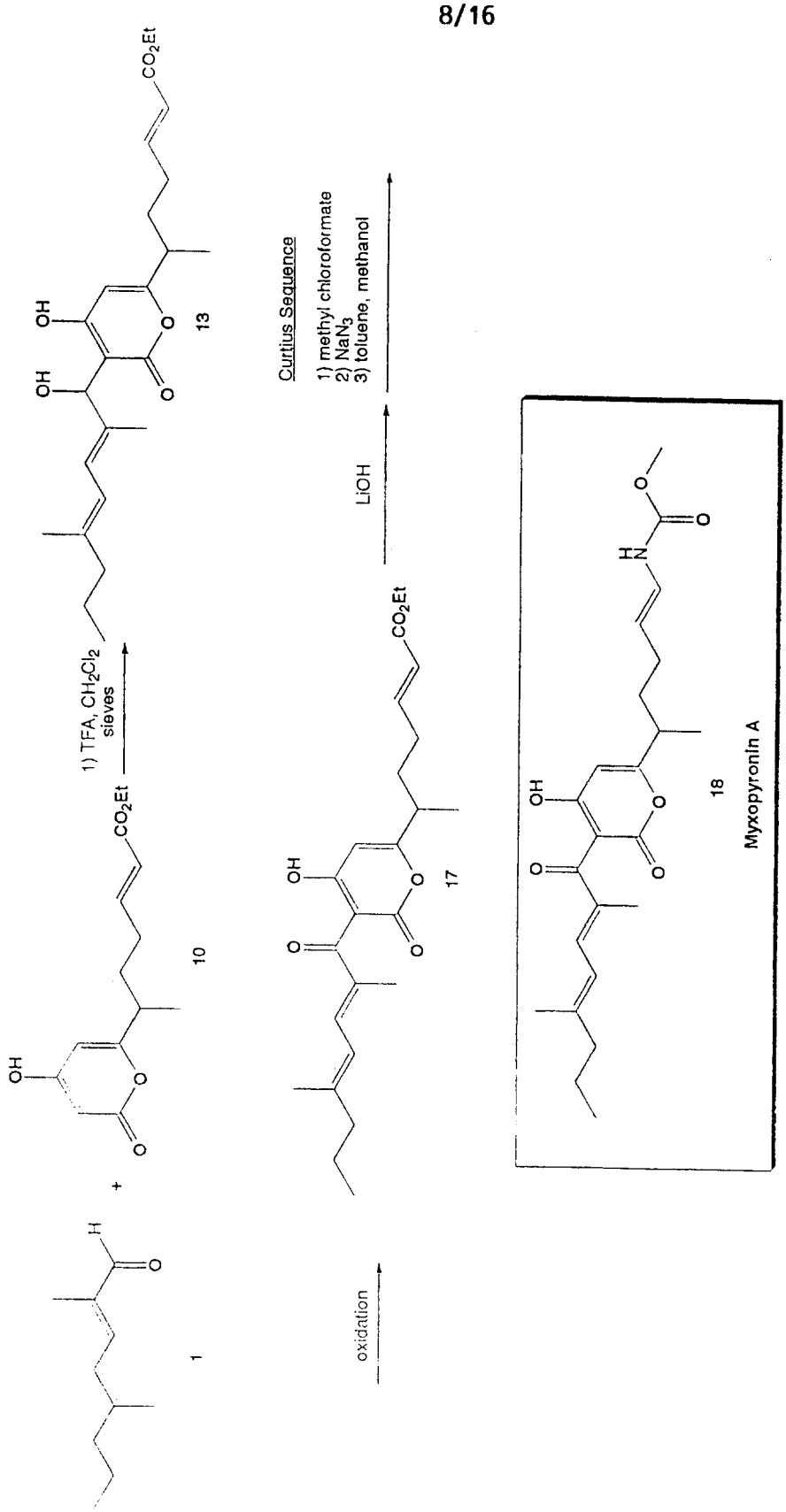

1) TFA, CH_2Cl_2
sieves
oxidation
LiOH
Curtius Sequence
1) methyl chloroformate
2) NaN_3
3) toluene, methanol
Myxopyronin A

FIG. 8

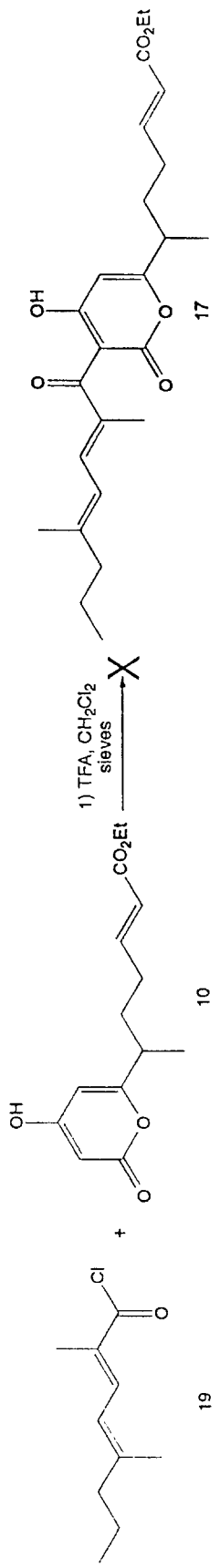


FIG. 9

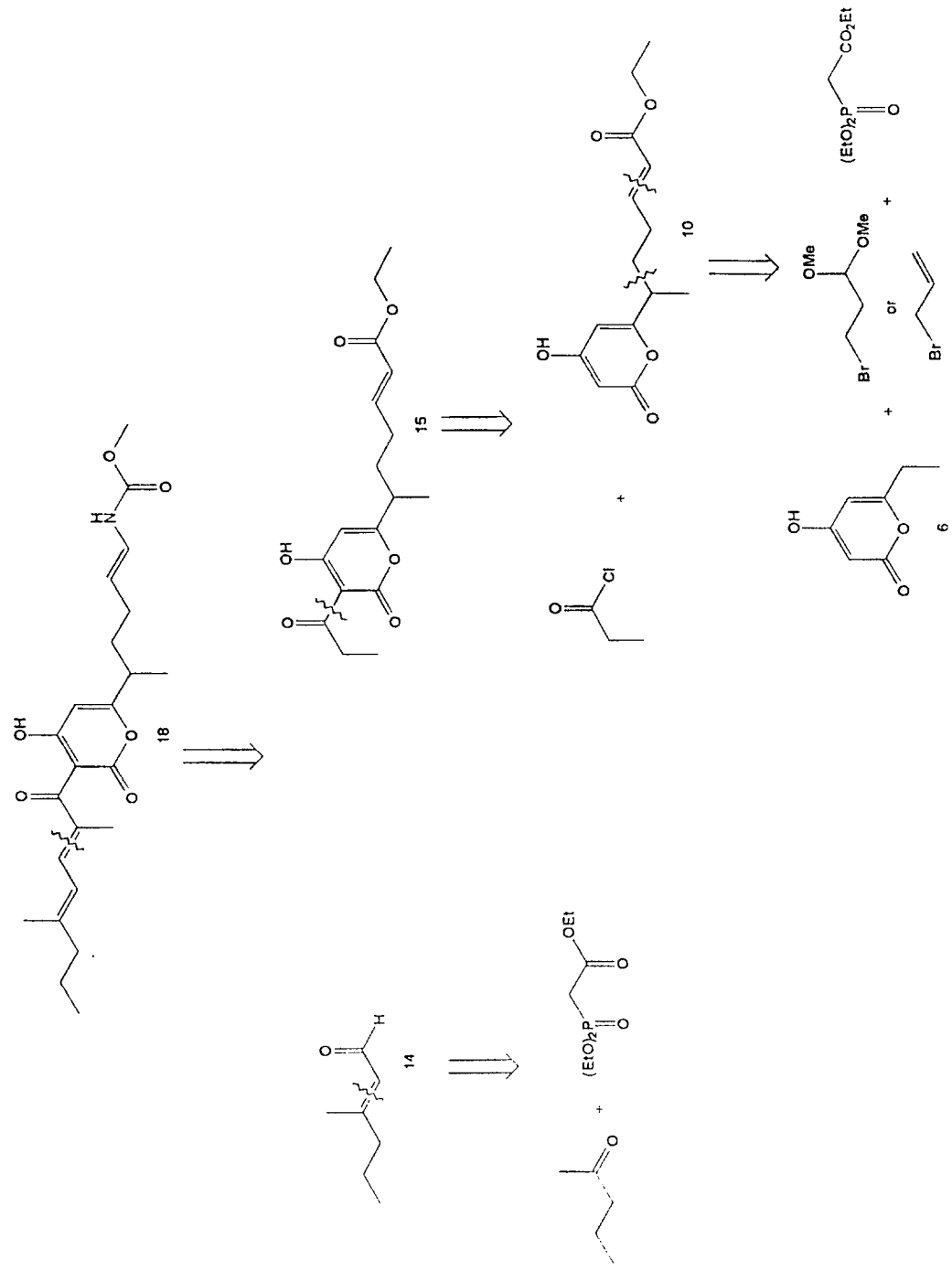


FIG. 10

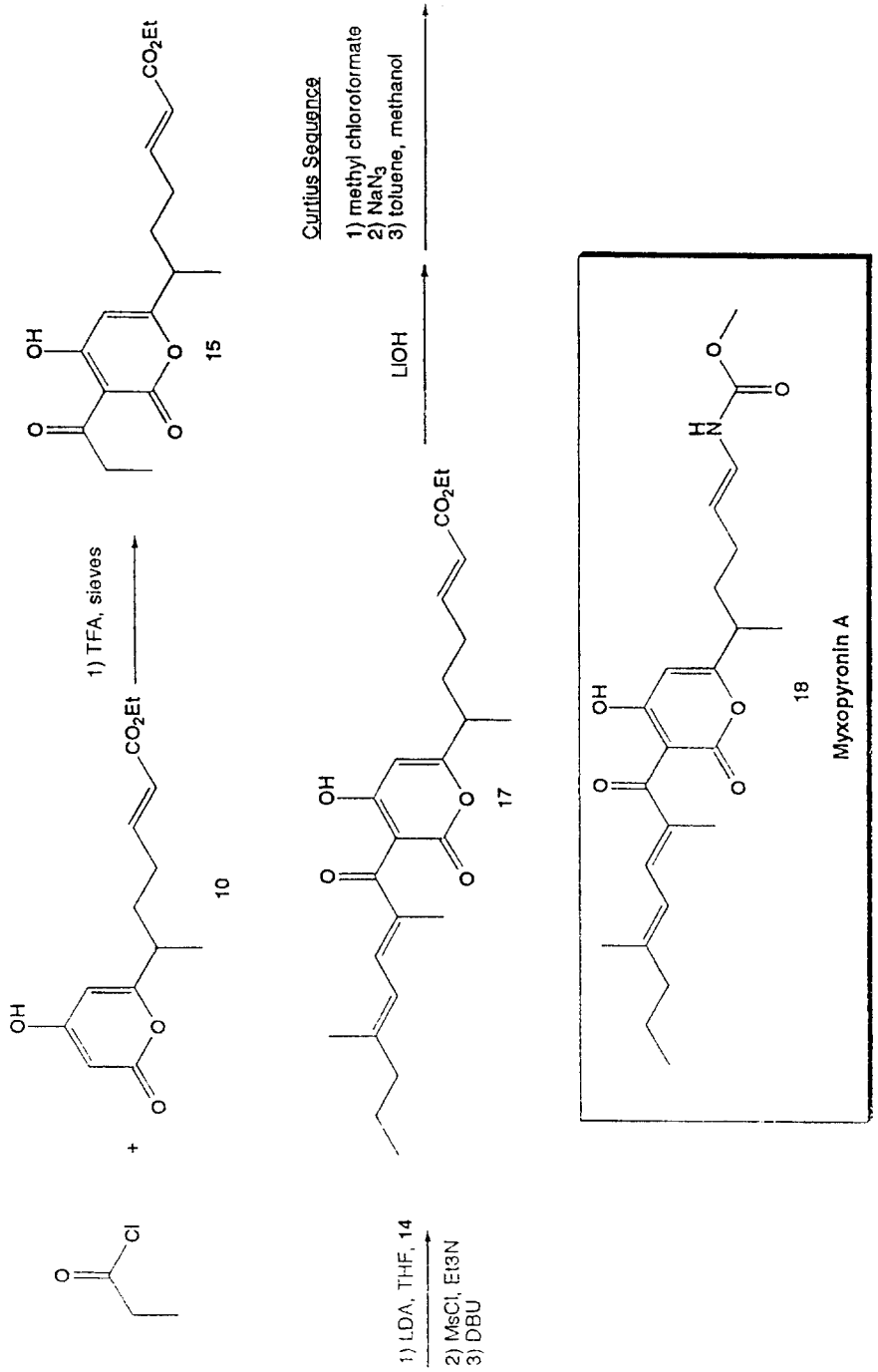

1) TFA, sieves
1) LDA, THF, 14
2) MsCl, Et3N
3) DBU
Curtius Sequence
1) methyl chloroformate
2) NaN3
3) toluene, methanol
LiOH
Myxopyronin A

FIG. 11

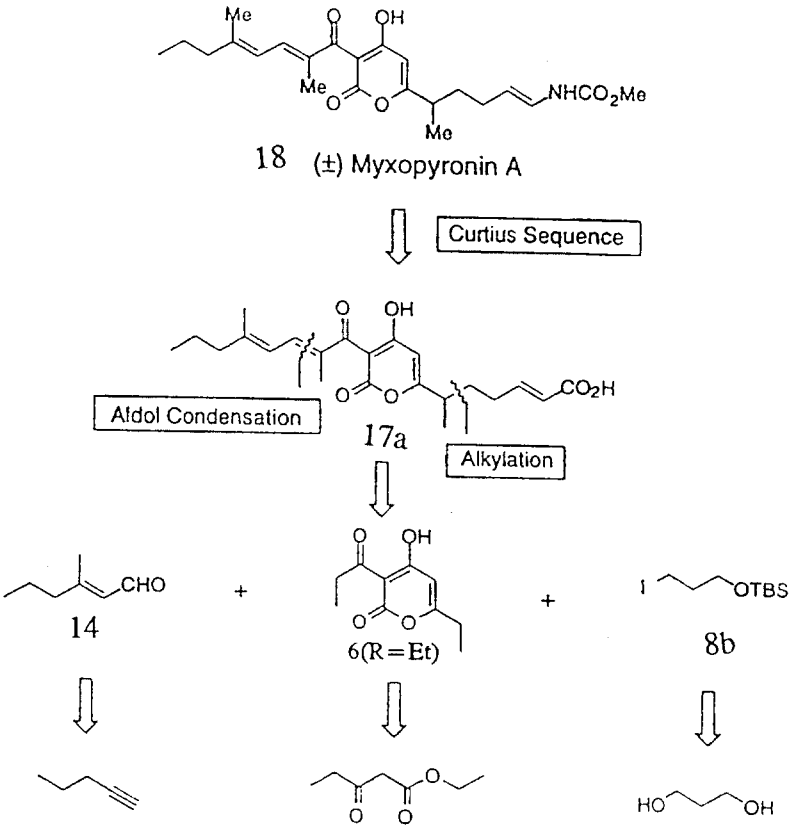

Me
O
OH
Me
O
O
NHCO2Me
Me
18 (±) Myxopyronin A
Curtius Sequence
O
OH
CO2H
Aldol Condensation
17a
Alkylation
CHO
14
+
O
OH
O
O
6(R=Et)
+
I
OTBS
8b
O
O
HO
OH

FIG. 12

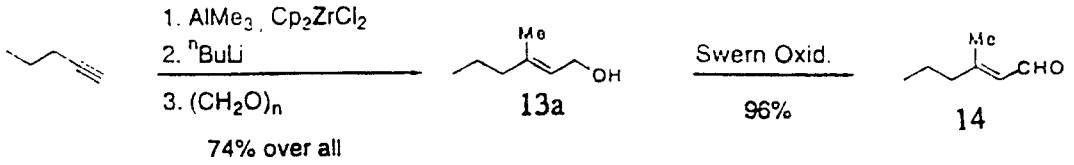


FIG. 12(a)

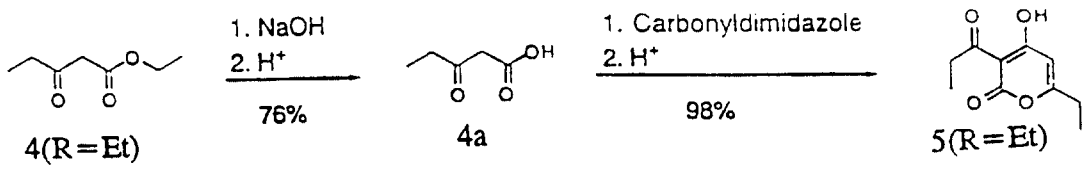


FIG. 12(b)

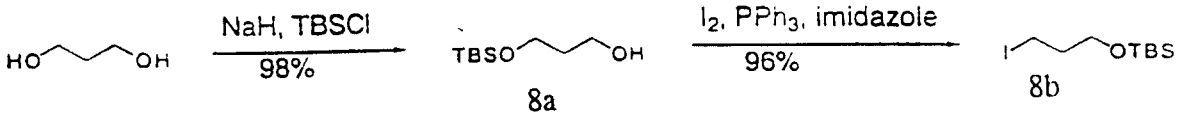


FIG. 12(c)

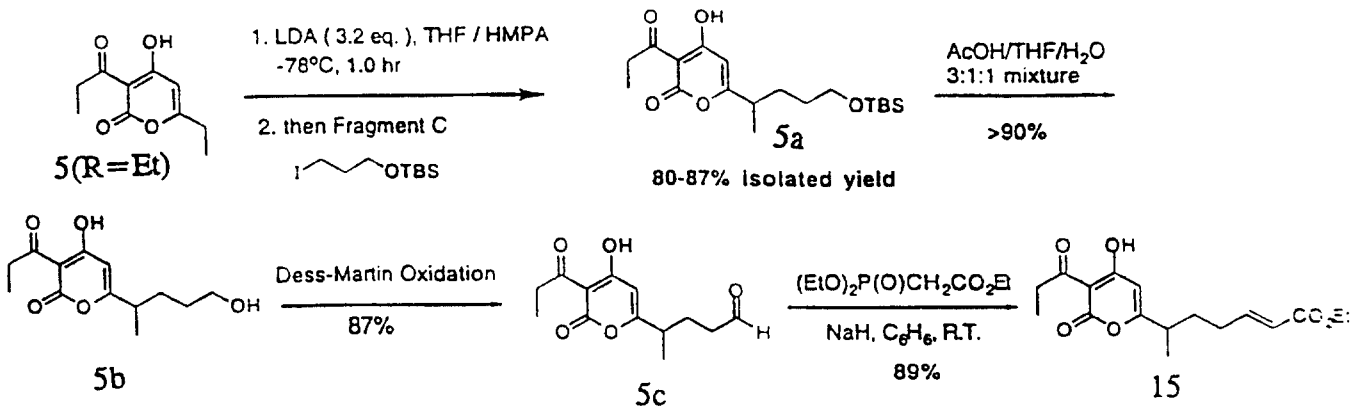


FIG. 13(a)

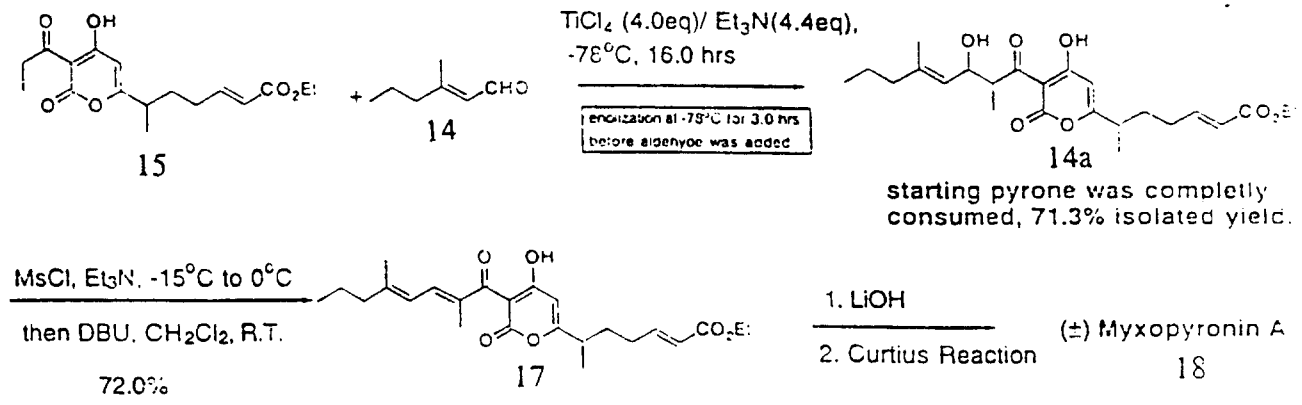
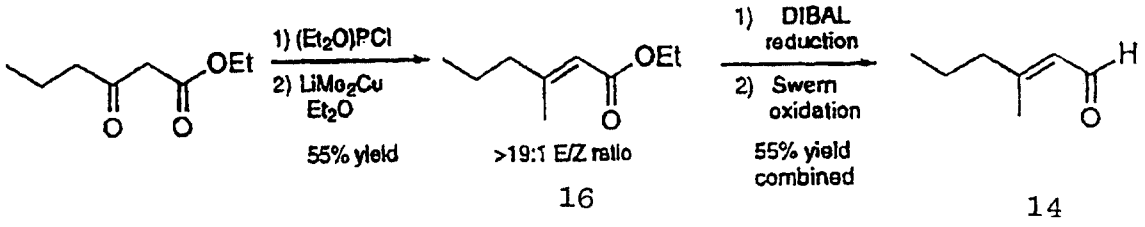
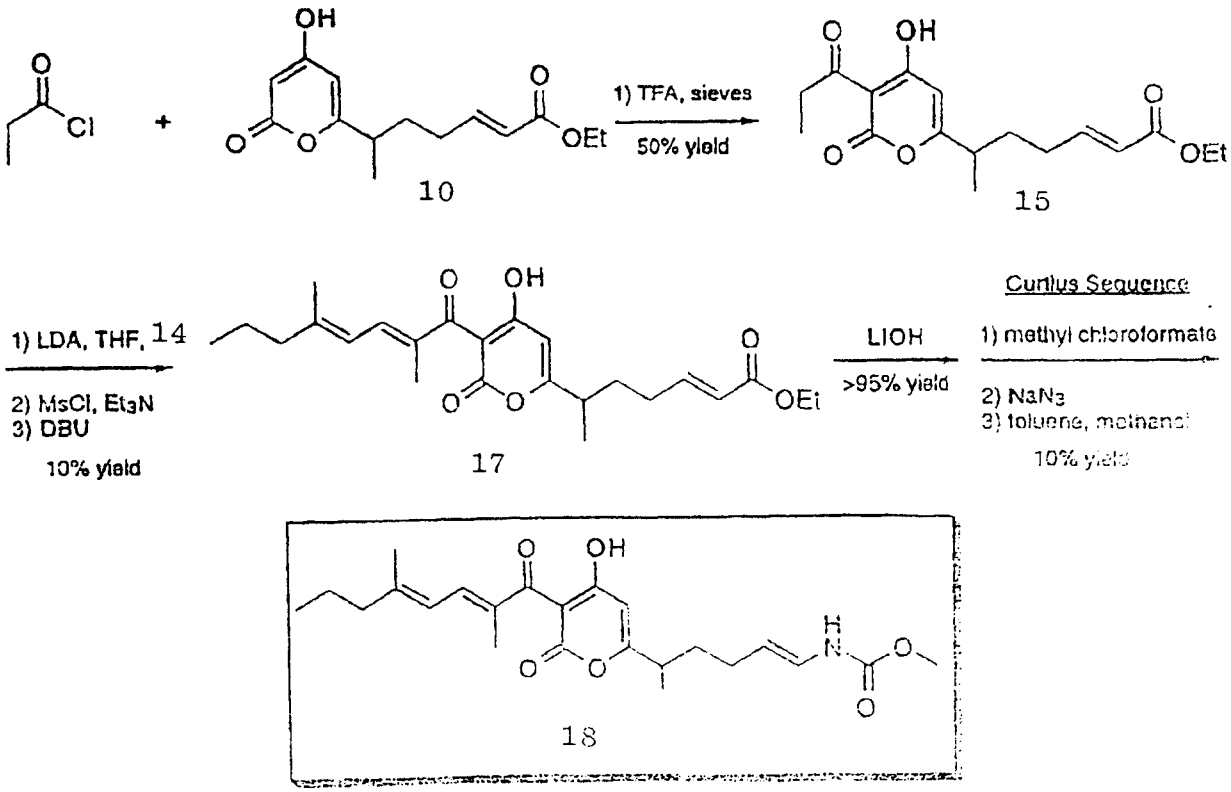


FIG. 13(b)



16 14

Fig. 14(a)



10 15 17

18

Fig. 14(b)

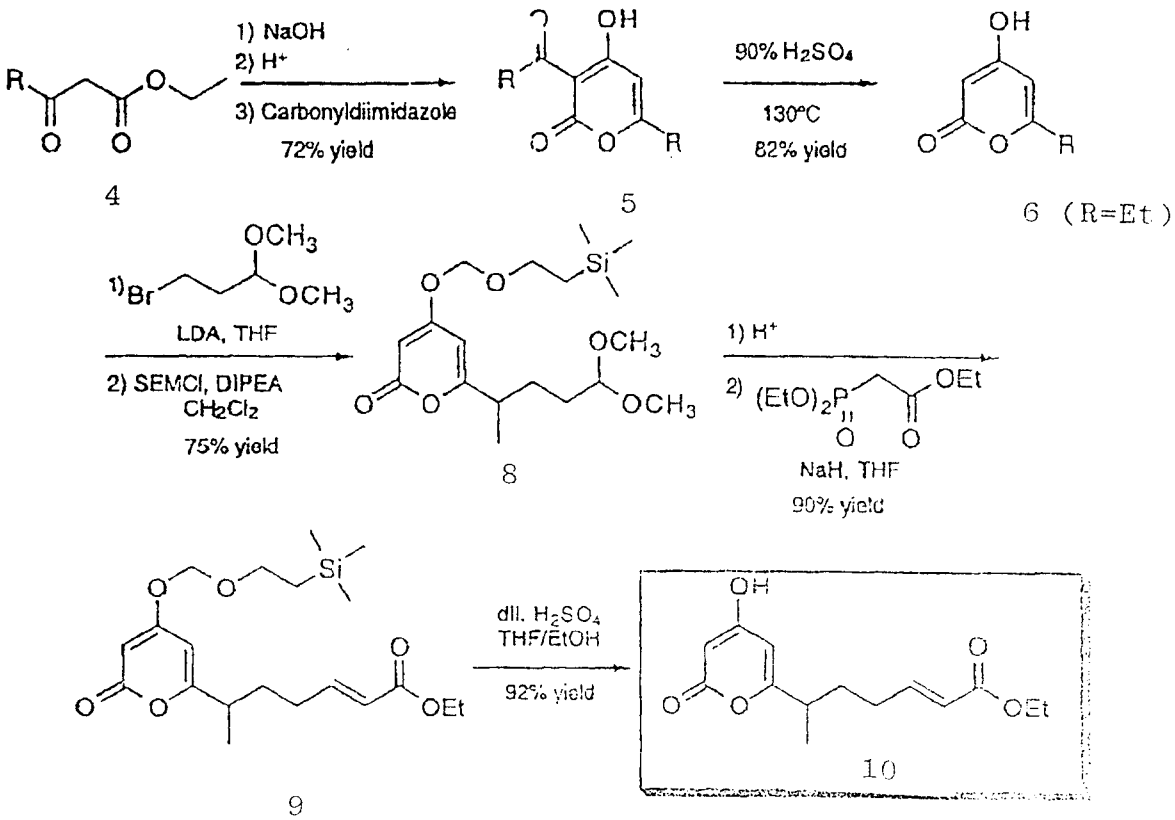

1) NaOH
2) H+
3) Carbonyldiimidazole
72% yield
90% H2SO4
130°C
82% yield
4
5
6 (R=Et)
1) Br
OCH3
OCH3
LDA, THF
2) SEMCl, DIPEA
CH2Cl2
75% yield
8
1) H+
2) (EtO)2P
OEt
NaH, THF
90% yield
dil. H2SO4
THF/EtOH
92% yield
9
10

Fig. 15