1994

Total synthesis of pyranonaphthoquinone natural products

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Total synthesis of pyranonaphthoquinone natural products

Li, Jun, Ph.D.

Iowa State University, 1994

Total synthesis of pyranonaphthoquinone natural products

by

Jun Li

A Dissertation Submitted to the

Graduate Faculty in Partial Fulfillment of the

Requirements for the Degree of

DOCTOR OF PHILOSOPHY

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Signature was redacted for privacy.
In Charge of Major Work

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For the Major Department

Signature was redacted for privacy.
For the Graduate College

Iowa State University
Ames, Iowa

1994

DEDICATION

To my parents, wife and son

TABLE OF CONTENTS

GENERAL INTRODUCTION

Organic synthesis remains one of the most challenging fields of chemistry. The key aspect of organic synthesis is finding the most efficient synthetic route. New methodology developed in organic synthesis can sometimes greatly improve the synthetic efficiency. This dissertation will deal with both the development of new methodology, as well as the total synthesis of pyranonaphthoquinone natural products.

Explanation of the Dissertation Format

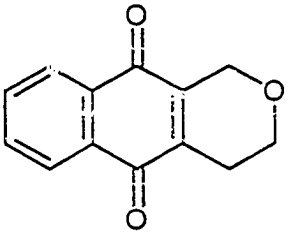
This dissertation is divided into two separate papers, each in publishable format. The structures and references for each are therefore numbered independently. Each paper is preceded by an introduction. The first paper covers the enantioselective total synthesis of frenolicin B and α, β-epoxyfrenolicin B, and the total synthesis of racemic kalofungin. The second paper deals with the total synthesis of racemic hongconin. A general summary of both papers will follow the second paper.

PAPER I.

REGIOCONTROL BY REMOTE SUBSTITUENTS. TOTAL SYNTHESIS OF KALAFUNGIN, FRENOLICIN B, α,β-EPOXYFRENOLICIN B AND THEIR ANALOGS

INTRODUCTION

The pyranonaphthoquinone natural products are a growing class of compounds isolated from various species of *streptomycin*.[1] Members of this family exhibit a variety of biological activities.[2] Important members of this family include such as nanaomycins, kalafungin, frenolicin B, frenolicins, arizonins, and more complex analogs, such as the granticins, griseusins and SCH-38519. All of these compounds share a common isochromanquinone skeleton **1**.

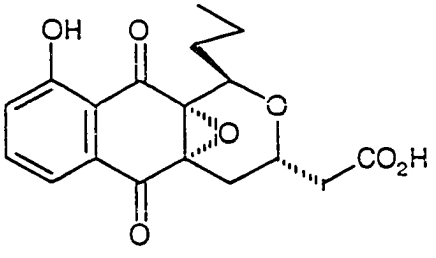


1

Isolation and Biological Activities of Pyranonaphthoquinone Antibiotics

Frenolicin (**2**) was isolated as pale yellow needles from *Streptomyces fradiae* in 1960.[3] The structure and relative stereochemistry were determined using spectroscopic data by Ellestad and co-workers.[4] Deoxyfrenolicin (**3**) was isolated from *Streptomyces roseofulvus* in 1978 by Iwai and co-workers.[5] The probable structure of deoxyfrenolicin was

deduced from spectra, and confirmed by direct comparison with a sample previously obtained by the chemical transformation of frenolicin. Optical rotatory dispersion studies on



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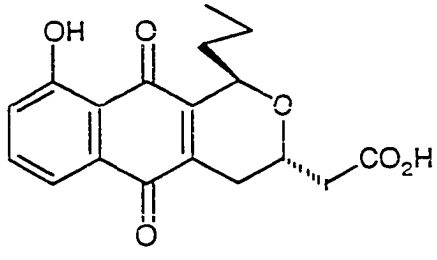
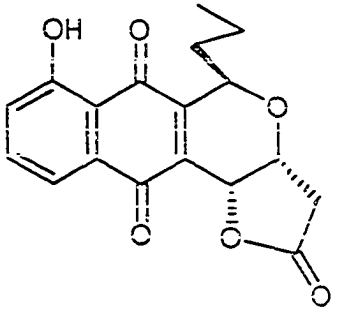
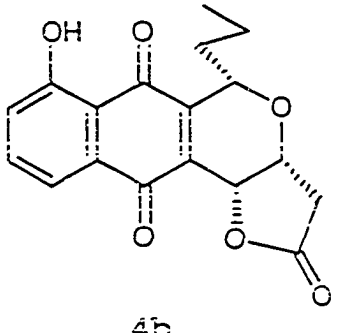


3

deoxyfrenolicin established the absolute configuration since deoxyfrenolicin shows same positive Cotton effect like kalafungin. At same time, Iwai et al. also found a new antibiotic designated as frenolicin B (**4a**) and its structure contained a lactone. In the primary biological test,



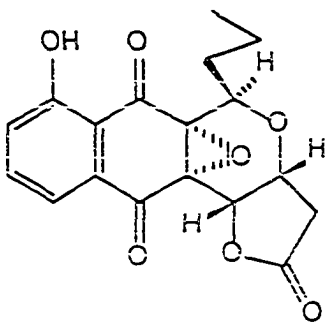
4a



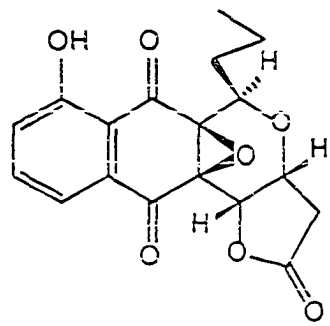
4b

deoxyfrenolicin was found more active against fungi than frenolicin.[5] Frenolicin B exhibited the highest antifungal activity at low concentration. Omura and co-workers found that frenolicin B exhibited excellent anticoccidial activity.[6] In their test, frenolicin B showed excellent protective effects against *Eimeria tenella* and proved comparable to *salinomycin* which is a polyether antibiotic used in the treatment of coccidial infections of poultry. The lack of the lactone portion such as in deoxyfrenolicin resulted in substantial inactivation. The epimerization at C-5 on the pyran ring of frenolicin B, such as **4b**, brought about the reduction of the activity.

Recently, scientists from Hoffmann-LaRoche found two new frenolicin B analogs, α-epoxyfrenolicin (**5a**) and β-epoxyfrenolicin B (**5b**). They also reported many interesting results about the bioactivity of frenolicin B and its analogs.[7]

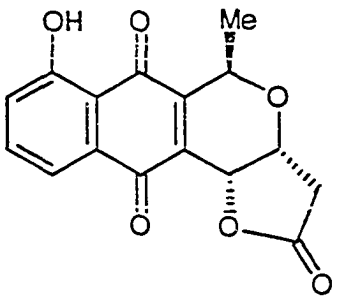


5a



5b

Kalafungin (**6**) was extracted from the fermentation broth of *Streptomyces tanashiensis* strain Kala, and purified by chromatography on silica gel followed by crystallization.[8] The structure was determined by spectra and single crystal X-ray analysis.[8,9] The absolute stereochemistry of



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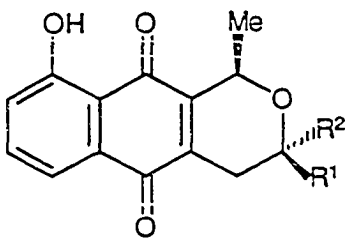
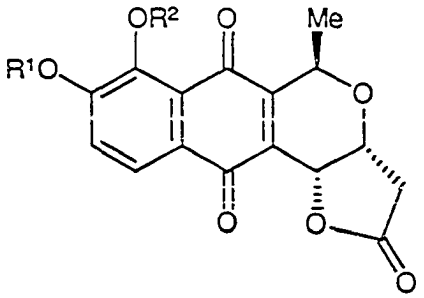


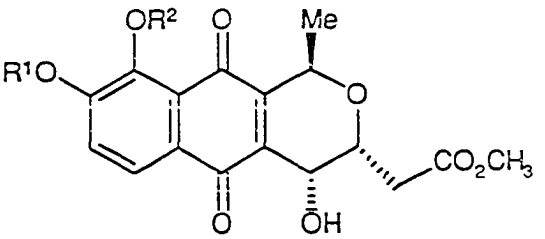
7a: R^1=Me, R^2=H
7b: R^1=H, R^2=Me

kalafungin was assigned by optical rotatory dispersion comparisons with the known substances eleutherin (**7a**) and isoeleutherin (**7b**).[8] Clinical testing has shown that kalafungin is inhibitory in vitro against a variety of pathogenic fungi, yeast, protozoa, and gram-positive and gram-negative bacteria.[10]

Antibiotic arizonins (**8**) and (**9**) were discovered by Hochlowski and co-workers in 1987.[11] These antigram-positive antibiotics were produced by the fermentation of *Actinoplanes arizonaensis* sp. nov. Spectral studies characterized these compounds as kalafungin-type antibiotics.



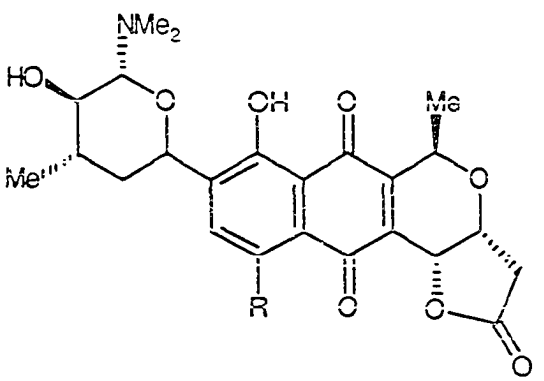
8a: R^1=H, R^2=Me
8b: R^1=Me, R^2=H
8c: R^1=Me, R^2=Me



9a: R^1=H, R^2=Me
9b: R^1=Me, R^2=H
9c: R^1=Me, R^2=Me

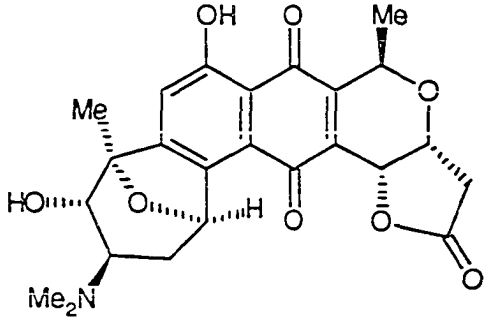
They differ from other pyranonaphthoquinones by an unusual oxidation pattern on the aromatic ring. Their structures are shown above.

Medermycin (**10a**) and mederrhodin A (**10b**) are similar to the kalafungin in absolute configuration and exhibit low acute toxicity in mice and appear promising as antitumor agents.[12,13]



10a: R=H
10b: R=Me

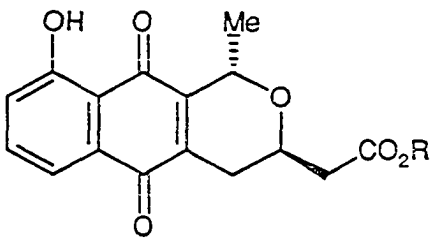
A more complex antibiotic, SCH 38519 (**11**), was isolated from a novel *Thermomonospora* species. SCH 38519 inhibits the growth of gram positive and gram negative microorganisms. The structure and absolute stereochemistry of SCH 38519 were determined by NMR spectrum and single crystal X-ray analysis of its hydrochloride salt.[14]



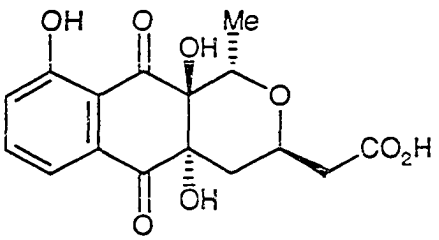
11

The nanaomycin (NNM) subclass is the largest group of the pyranonaphthoquinone antibiotics and has been well studied. Nanaomycin A (**12a**) and nanaomycin B (**12b**) were first isolated from a soil sample and designated *Streptomyces rose* var. notoensis by Omura and coworkers in 1974.[15,16] Nanaomycin A and B inhibit mainly mycoplasmas, fungi and gram-positive bacteria. The acute toxicities (LD_{50}, ip) of **12a** and **12b** in mice are 28.2 and 169 mg/kg, respectively. Later, nanaomycins C, D, and E were also found from the same strain by this group.[17,18,19] Nanaomycin C (**12c**) is an amide of nanaomycin A and exerts as strong activity against gram-

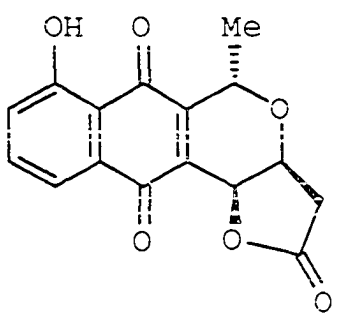
positive bacteria as nanaomycin A, but weaker activity against fungi and mycoplasmas than nanaomycin A. Interestingly, nanaomycin D (**12d**) is the enantiomer of kalafungin which we mentioned before. Antimicrobial activities of nanaomycin E are weaker than those of nanaomycin A. The mode of action of nanaomycin D and A on a gram-negative marine bacterium *Vibrio alginolyticus* was also studied by Omura's group. Their studies showed that nanaomycin D had a higher growth



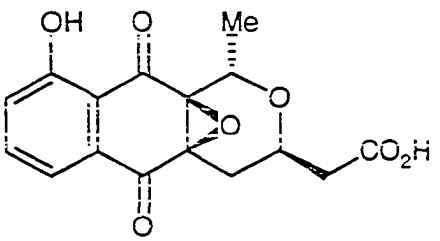
12a: R=H
12c: R=NH_2



12b



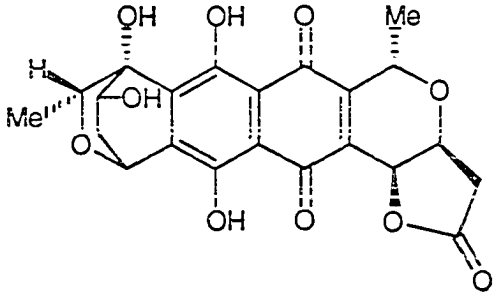
12d



12e

inhibitory activity than nanaomycin A against a gram-negative marine bacterium, *Vibrio alginolyticus*. These quinone activities were reduced by the respiratory chain-linked flavin dehydrogenase of the organism, and the reduced form of nanaomycins were quickly autoxidized by molecular oxygen to produce superoxide radicals. The growth inhibitory activities of nanaomycin A and D were partly reduced by raising the superoxide dismutase level of the cells. Thus, the ability to produce O_2^- at the cell membrane was correlated to the antibacterial activities of nanaomycin A and D.

More complex members of the pyranonaphthoquinone family also exist. Granaticin (litmomycin) (**13**) was isolated from

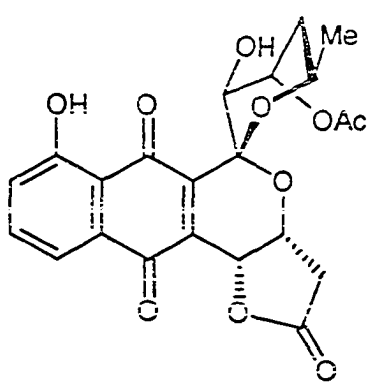


13

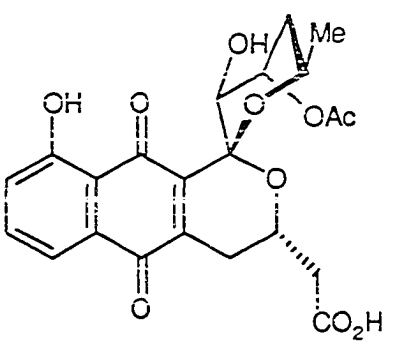
Streptomyces species, *S. litmogenes*.[20a,20b] Its structure was clarified by a combination of chemical degradation and an X-ray analysis in 1968.[21a,21b] Granaticin is highly active

against gram-positive bacteria (MIC 0.25~1.75 μg/ml), but has little or no activity against gram-negative bacteria.[22,23] It can inhibit leucyl-transfer ribonucleic acid syntheses and interfere with the charging process of leucine tRNA in *Bacillus subtilis*.[24] The cytotoxicity of granaticin is attributed to inhibition of ribosomal RNA maturation. Antitumor activity against P-388 lymphocytic leukemia in mice was also observed.[25]

Griseusins A (**14a**) and B (**14b**) were isolated from a strain of Streptomyces griseus, and their structures were determined by spectroscopic analysis.[26a,26b] Griseusins are also active against gram-positive bacteria *in vitro*, but showed no survival effect in mice infected with *Streptococus pyogenes* and *Diplococcus pneumoniae*.



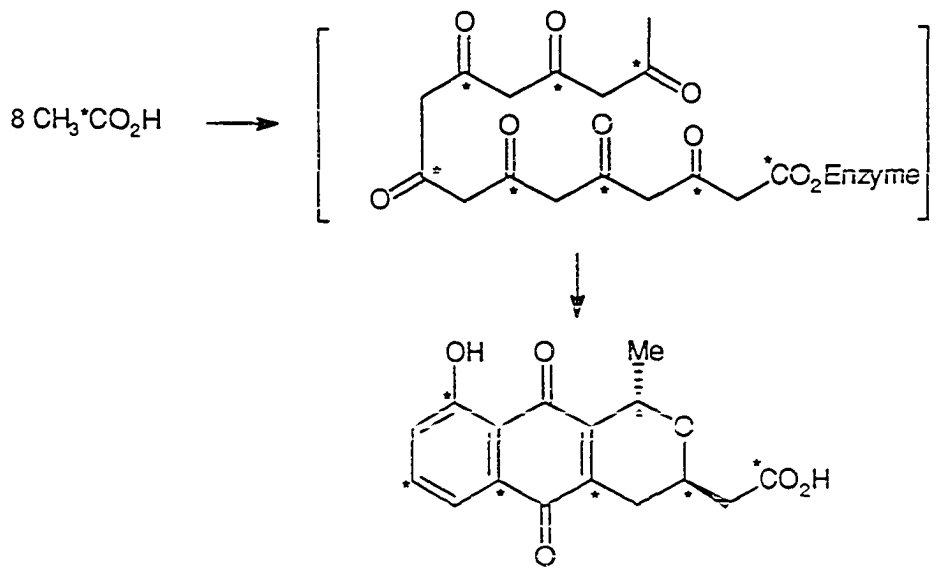
14a



14b

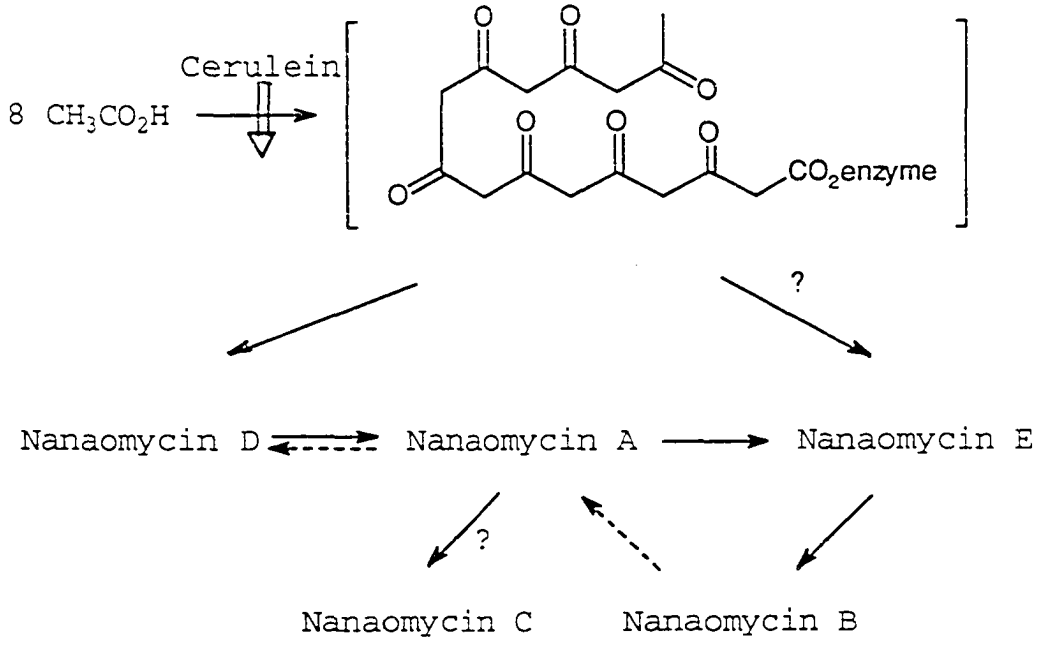
Biosynthesis of Pyranonaphthoquinone Antibiotics

Details of the biosynthesis of some pyranonaphthoqunones have also been studied. The biosynthetic origin of nanaomycin was studied by Tanaka et al.[27] using ^{13}C-labeled acetate and ^{13}C-NMR spectroscopy. It was established that the carbon skeleton of nanomycin was derived from eight acetate units.

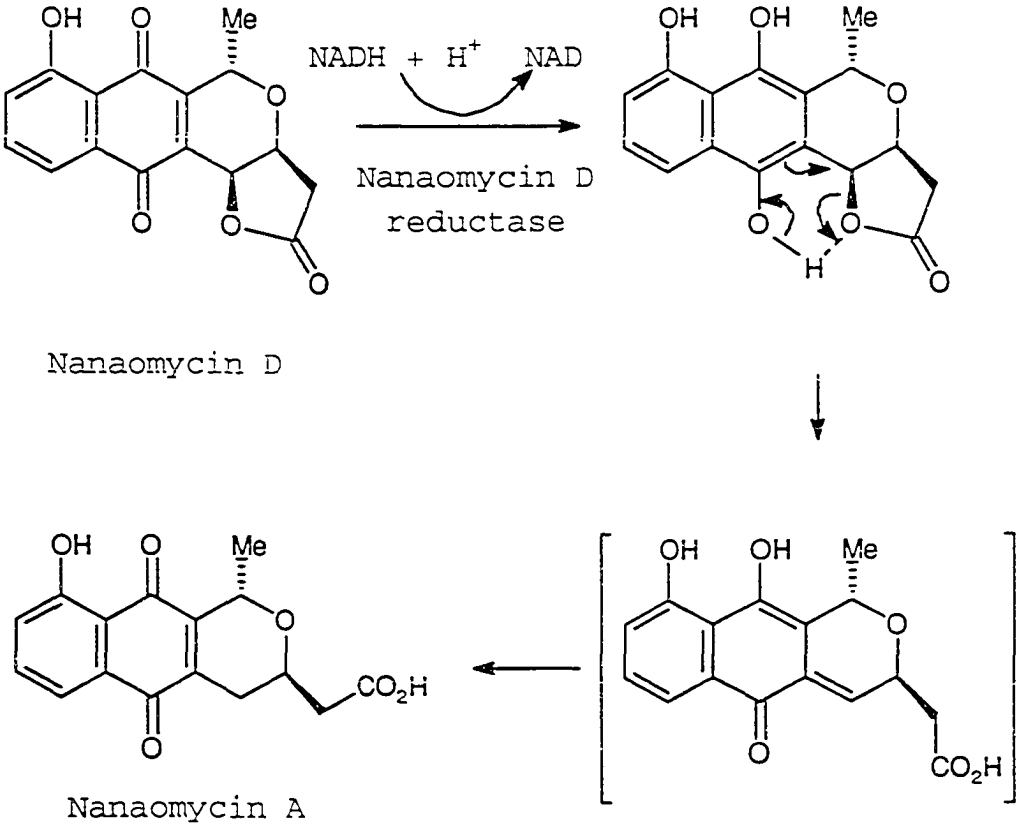


A further study indicated that nanomycin D was considered to be the first component produced from the hypothetical intermediate "polyketide". By studying the biosynthetic relation of the nanaomycins produced from *Strepomyces rose* var. *notoensis*, Omura et al.[28] proposed

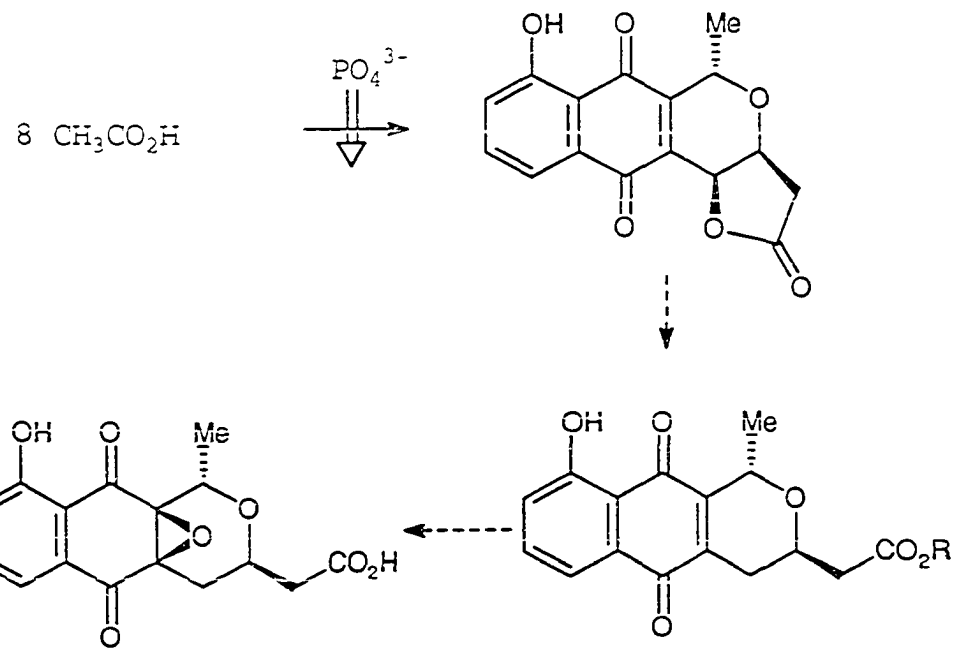
that the biosynthetic sequence for the nanaomycin is: nanaomycin D→nanaomycin A→nanaomycin E→nanaomycin B.



It was found that nanaomycin D reductase which is involved in the biosynthesis of the antifungal antibiotic nanaomycin catalyzes the formation of nanaomycin A from nanaomycin D in the presence of NADH under anaerobic conditions. On the other hand, under aerobic conditions NADH is consumed and nanaomycin A formation is markedly reduced. In fact, nanaomycin D reductase is an NADH dehydrogenase (quinone).[29]



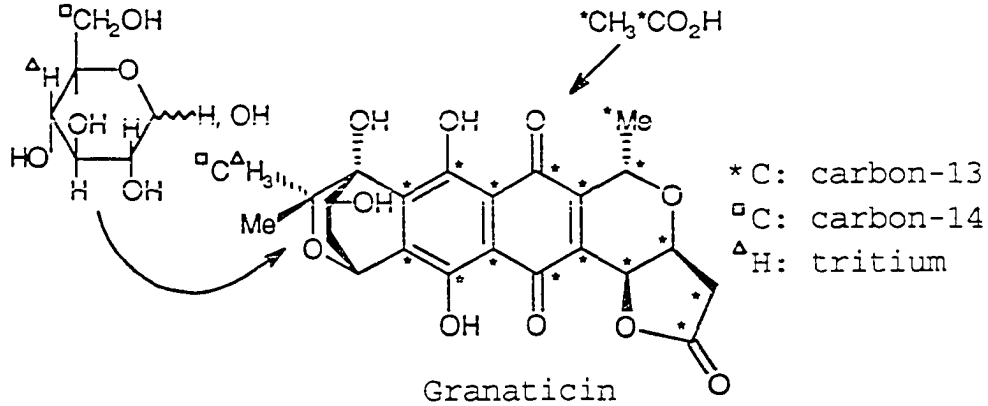
Furthermore, it was found that the production of nanaomycins and other antibiotics can be controlled under some conditions. Nanaomycin production by *Strepyomyces rosa* subsp. *notoensis* in complex media was inhibited by exogenously supplied inorganic phosphate. The inhibition was reversed by phosphate-trapping agents, such as allophone aluminum oxide.[30] It was also found that the site of regulation of nanaomycin biosynthesis by inorganic phosphate lies within the steps between acetate and nanaomycin D.[31]



⟵ : steps sensitive to PO_4^{3-} effect

⟵ - - - : steps insensitive to PO_4^{3-} effect

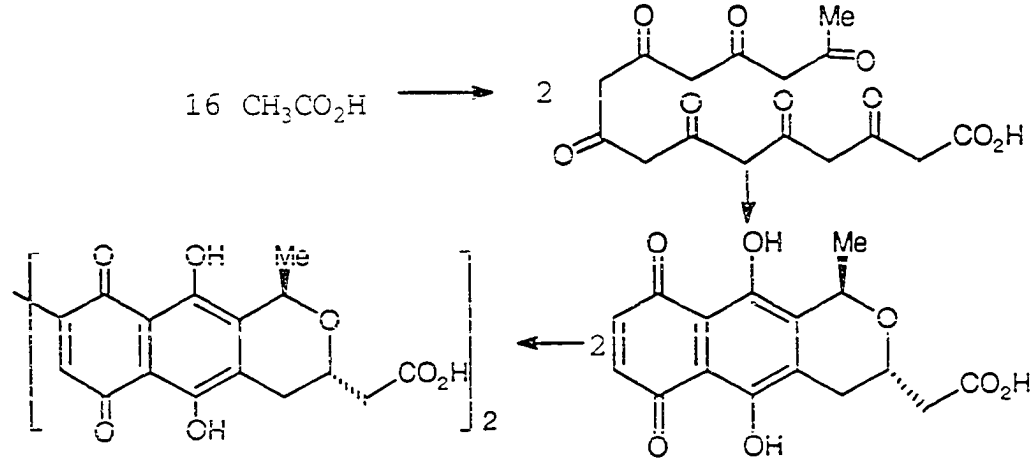
Biosynthesis of the more complex antibiotic granaticin was achieved by Floss and co-workers of Purdue University in 1979.[32] Granaticin is synthesized by *Streptomyces violaceoruber* from eight acetate units, which are assembled into a benzoisochromanquinone moiety, and a molecule of glucose, which is converted into a 2,6-dideoxyhexose and attached to the aromatic moiety by carbon-carbon linkages. The five-membered lactone ring moiety is derived enzymatically by oxidation of the reduced component, dihydrogranaticin.



Granaticin

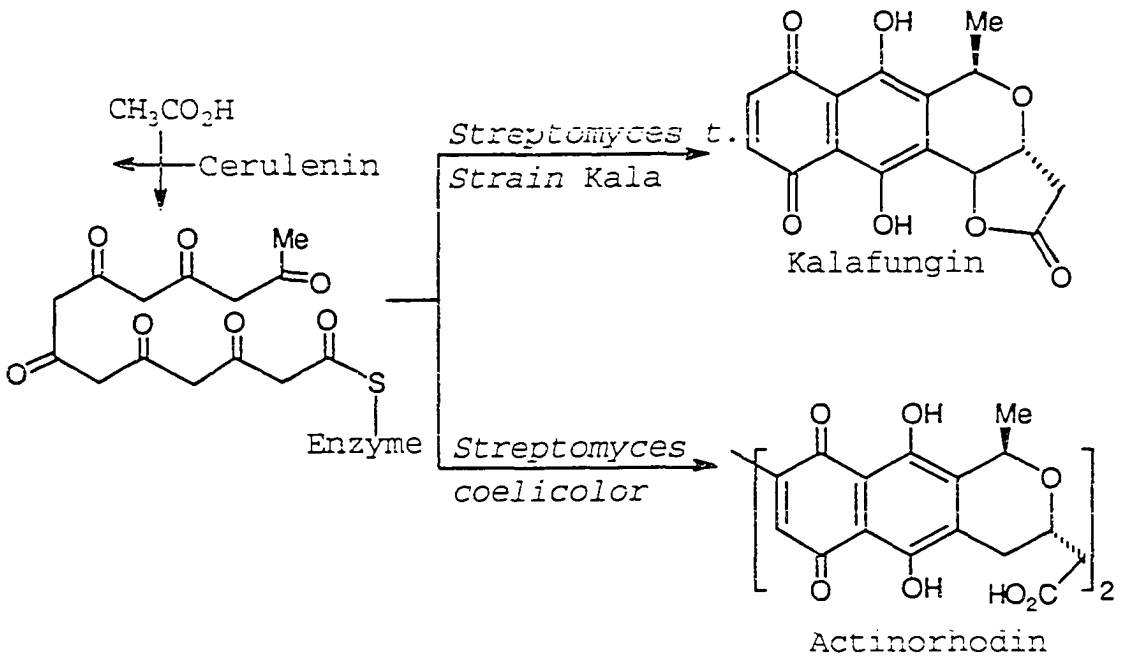
The dimeric isochromanquinone actinorhodin(16) can also be biosynthesized from simple acetate. [1,2-^{13}C]Acetate feeding experiments revealed that actinorhodin is a polyketide-derived antibiotic originating from 16 acetate units.[33]

Although kalafungin is an intermediate or shunt product in actinorhodin biosynthesis in *S. coelicolor A3(2)*, the genes for kalafungin biosynthesis in *S. tanashiensis* are not



15 Actinorhodin

identical with those in actinorhodin biosynthesis *S. coelicolor A3(2)*.[34,35] However, they do share some genes in their biosynthesis. The order of these genes are similar to each other, but the spacing is not identical.



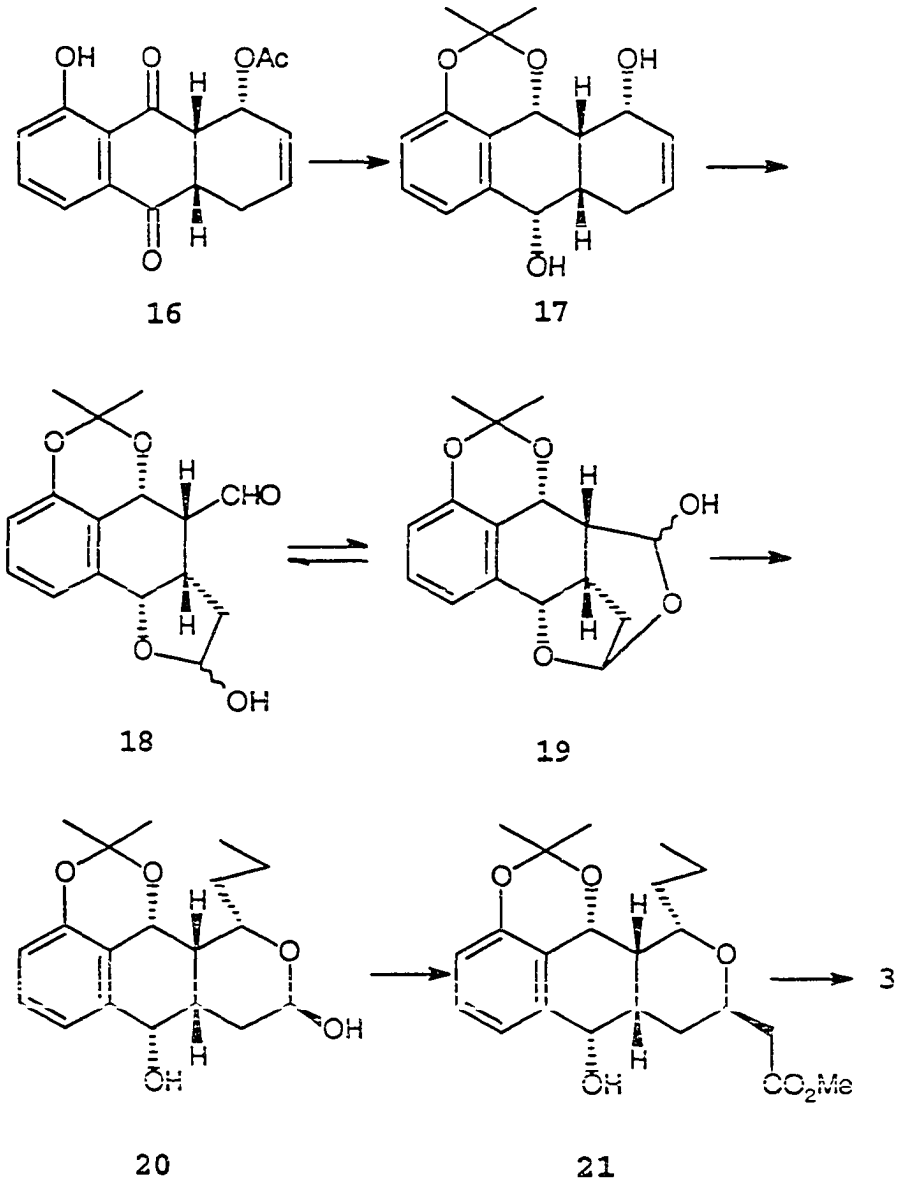
Technology of genetic engineering was also applied to the biosynthesis of pyranonaphthoquinone antibiotics. Novel antibiotics could arise through the transfer of biosynthetic genes between strepyomyces producing different antibiotics. The roduction of pyranonaphthoquinone antibiotics actinorhodin (**15**), granaticin (**13**), and medermycin (**10**) by genetic engineering was reported by Hopood et al.[36]

Chemical Synthesis of Pyranonaphthoquinone Antibiotics

The antimicrobial and antitumor activities of the pyranonaphthoquinones have attracted the considerable attention of organic chemists. To date, several antibiotics, such as kalafungin, nanaomycins, frenolicin, griseusin and related compounds have been synthesized. Many interesting strategies have been involved in these syntheses.

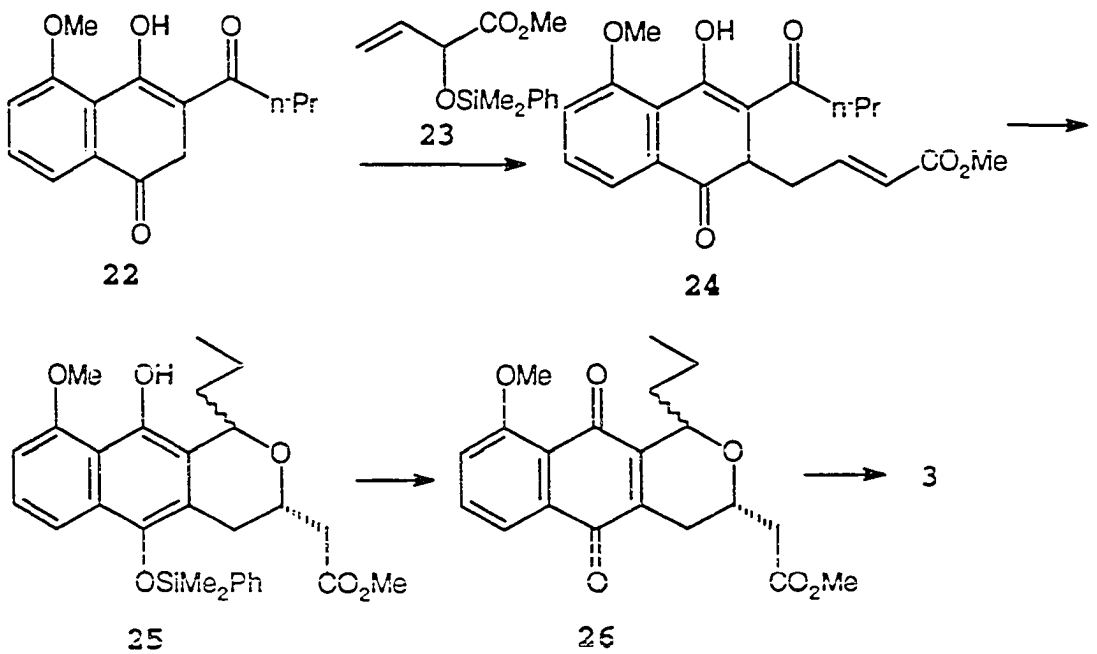
1. Synthesis of frenolicins

Frenolicin was first synthesized by Ichihara and co-workers in 1980.[37] In their synthesis, known compound **16** which was prepared from juglone and 1-acetoxy-1,3-butadiene was selected as the starting material. Reduction of **16** with sodium borohydride afforded the ketone alcohol, which was protected as its acetonide and then reduced further by lithium aluminum hydride (LAH) to diol **17**. Oxidative cleavage of the double bond using osmium tetroxide and sodium periodate followed by treatment with sodium borohydride afforded a key equilibrated mixture of **18** and **19**. Treatment of the mixture with *n*-propylmagnesium bromide gave the hemiacetal **20** stereoselectively. The Wittig-Horner reaction of **20** with diethylphosphonoacetate afforded the desired ester **21**. Oxidation of **21** with DDQ and TsOH followed by saponification led to deoxyfrenolicin **3**.



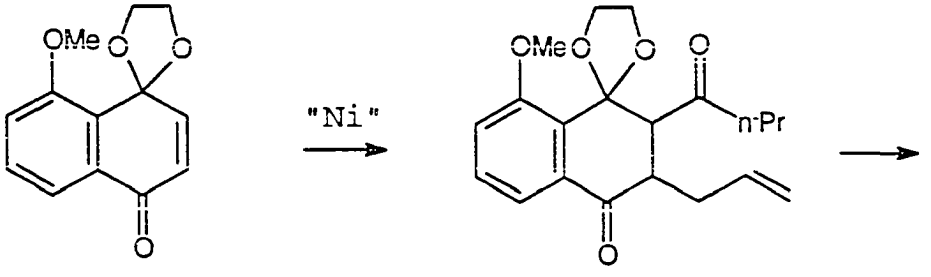
Naruta et al.[38] reported a shorter total synthesis of deoxyfrenolicin in 1982. The key step in the reaction sequence is the Lewis acid mediated Michael addition of **22** with methyl-(dimethylphenylsilyl)-3-butenoate (**23**). The conjugate adduct **24** was immediately silylated to the

corresponding TBDMS ether of **24**. Reductive cyclization of **24** afforded an isomeric mixture **25** which was oxidized with ceric ammonium nitrate (CAN) and demethylated by $AlCl_3$ to give epimers **26**. Acid catalyzed epimerization mainly afforded the desired isomer which was purified and hydrolyzed to afford **3**.

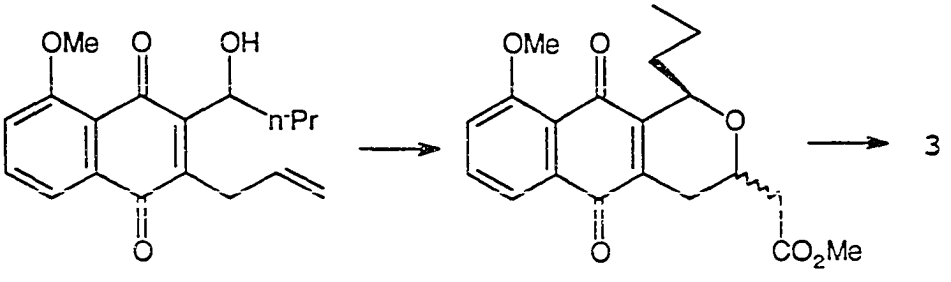


The strategies of conjugate addition/electrophile trapping with acylnickel carbonyl anions was used to synthesize deoxyfrenolicin.[39a,39b] This synthesis also started from a naphthoquinone derivative. Conjugate addition of the nickel complex followed by quenching with allyl iodide, provided the key intermediate **28**. Hydrolysis of the ketal, reduction of the side chain carbonyl, and oxidation converted

28 to the hydroxyquinone **29**. Reaction of **29** with Pd(II) and CO gas in methyl alcohol gave a mixture of **30a** and **30b**. Treatment of the phenol ethers with BBr_3 caused demethylation to the phenol. Isomerization of the cis isomer into the natural trans isomer was achieved by the method of Li.[47]



27 **28**

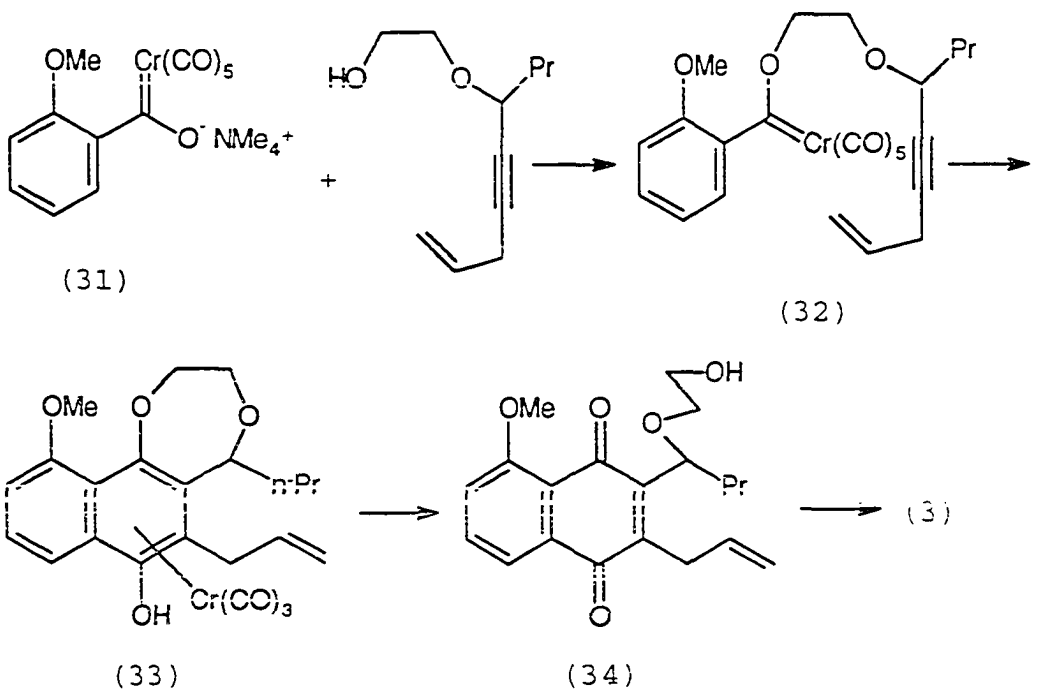


29

30a cis
30b trans

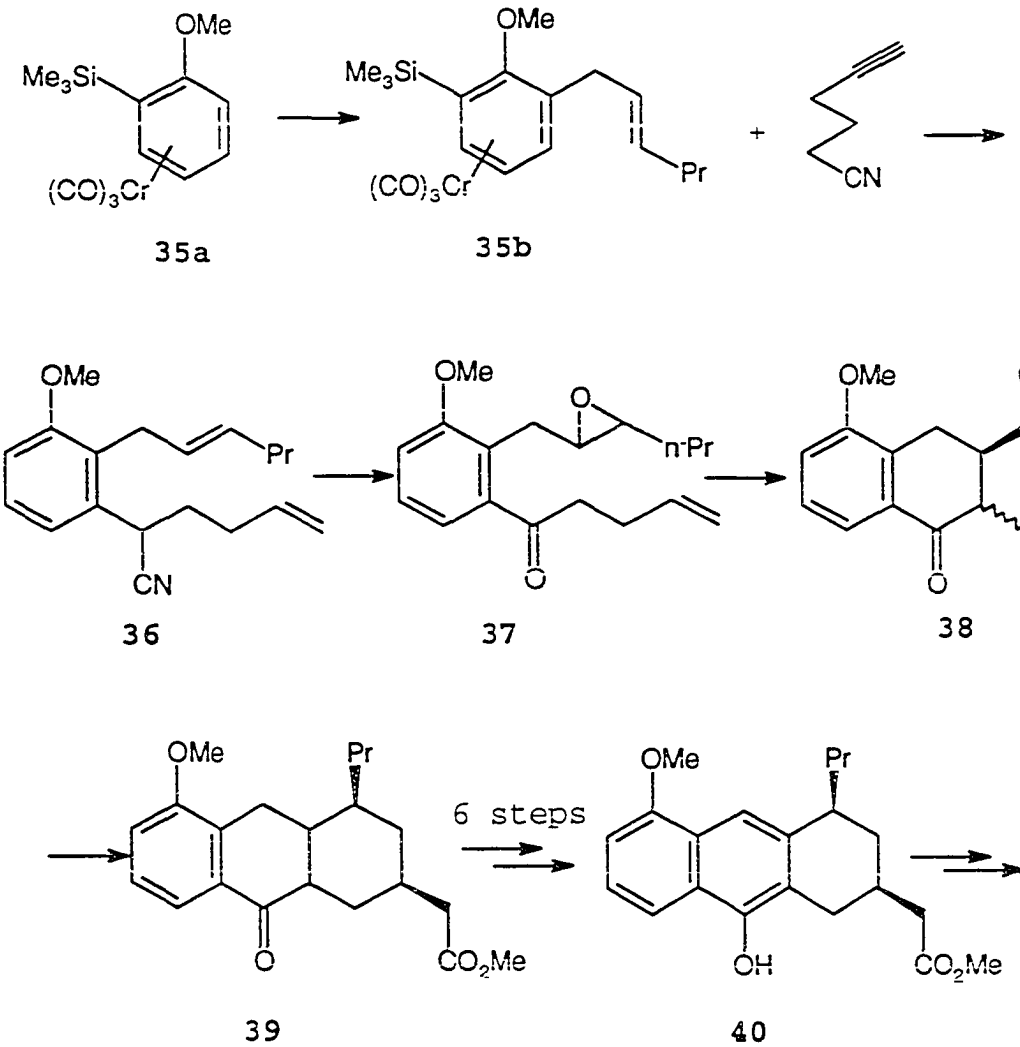
The above syntheses directly started from naphthoquinone derivatives and proceeded to construct the substituted dihydropyran ring. A different procedure beginning with a simple benzenoid derivative was reported by Semmelhack and co-workers.[40] Reaction of *o*-lithioanisole with chromium

hexacarbonyl gave a salt **31**. Coupling of compound **31** with an alkynol afforded the carbene complex **32** which cyclized at 35-37 °C to generate complex **33**. Removal of the chromium was achieved by treatment of the crude **33** with 2,3-dichloro-5,6-dicyanoquinone in aqueous acetonitrile, providing the 2,3-disubstituted naphthoquinone **34**. The rest of the synthesis was the same as the previous procedure.[39]



(31) (32) (33) (34)

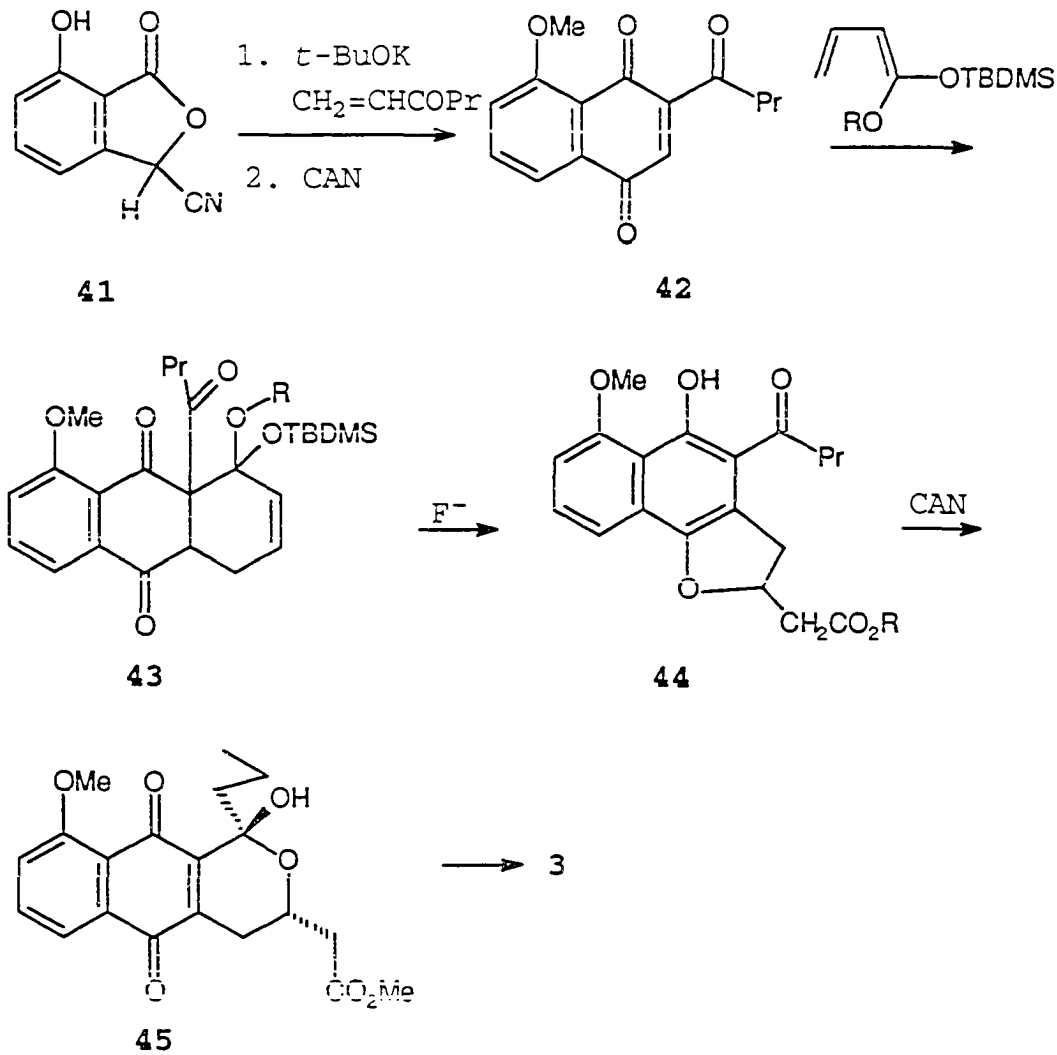
A similar procedure was also developed by Semmelhack and co-workers.[41] The crucial step was nucleophilic addition-oxidation with an arene-chromium complex to produce a 2,3-disubstituted anisole derivative **36**. The key to altering



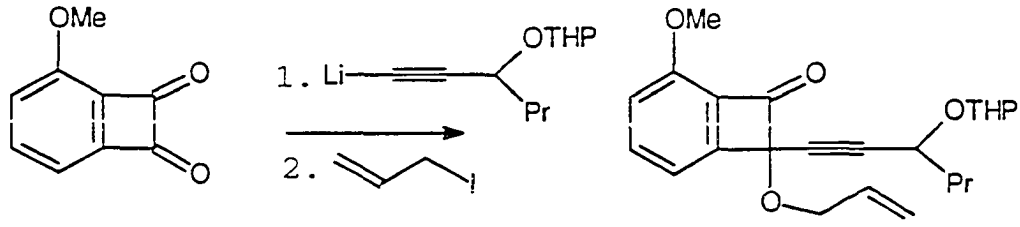
the selectivity in nucleophile addition to the anisole-$Cr(CO)_3$ complexes was the use of a trialkylsilyl group as a directing substituent. The metalation of **35a** using n-BuLi in ether proceeded smoothly and resulted in an o-lithio compound. The o-lithio intermediate could not be coupled with 2-hexenyl bromide directly. Instead, the copper derivative reacted with 2-hexenyl bromide to give **35b** in high yield. Addition of

secondary cyano-stabilized anion to the complex **35b,** followed by oxidation with excess iodine and desilylation gave the free substituted arene **36.** Oxidative decyanation converted **36** to corresponding ketone which was activated for ring closure by selective epoxidation to yield epoxide **37.** Treatment of the enol silyl ether (from **37**) with BBr_3 led to rapid formation of ring-closed products **38.** Pyran ring intermediate **39** was obtained by a Pd(II)/CO process and a multistep procedure (6 steps) was employed to convert **39** to cis compound **40.** A Jones oxidation converted naphthol **40** to a naphthoquinone with trans stereochemistry which was then converted to deoxyfrenolicin (**3**) by following the literature precedent.

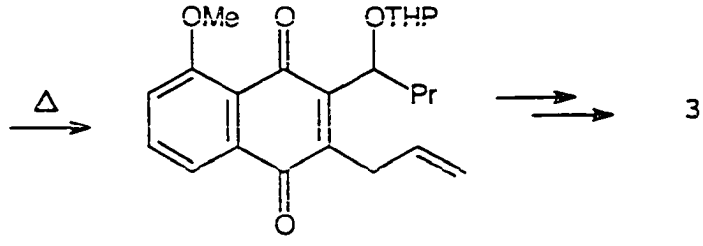
Kraus et al.[42] reported an efficient total synthesis of deoxyfrenolicin. The key steps in the synthesis include a phthalide annulation reaction to provide a substituted naphthoquinone. The synthesis of deoxyfrenolicin began with the reaction of **41** with propyl vinyl ketone. Oxidation of the resulting dihydroquinone to quinone **42** was followed by a tandem Diels-Alder/retro-Claisen reaction to produce the carbon skeleton **44.** Oxidation of **44** with ceric ammonium nitrate afforded quinone hemiketal **45.** A new stereoselective reduction of a hemiketal using ionic hydrogenation conditions (triethylsilane, trifluoroacetic acid) was also developed in this research, which afforded the target molecule **3.**



Recently, a formal synthesis of naphthoquinones which involves the thermal rearrangement of an alkynyl-substituted benzocyclobutenone was reported.[43] The reaction was employed as a key step in the synthesis of 2-(1-hydroxyethyl)- and 2-(1-hydroxybutyl)-8-methoxy-3-(2-propenyl)-1,4-naphthoquinones, which constitutes a formal synthesis of nanaomycin A and deoxyfrenolincin.



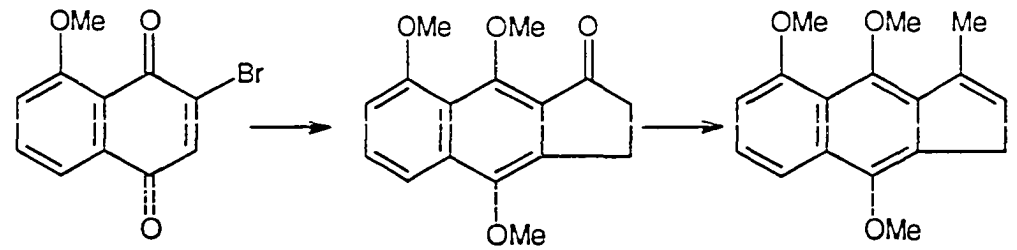
46 47



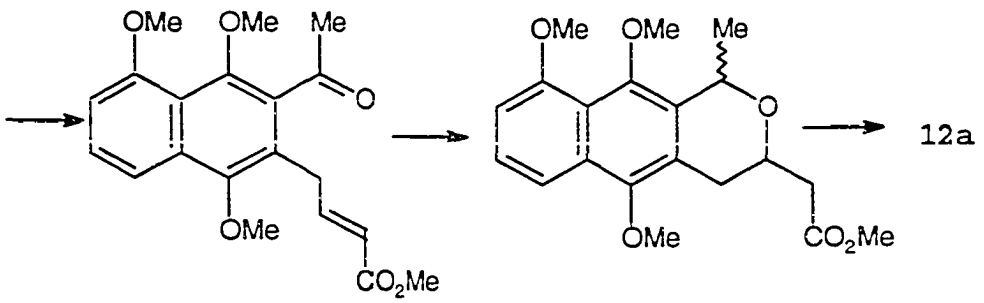
48

2. Synthesis of nanaomycins

Nanaomycin A (**12a**) has been synthesized by several methods used for deoxyfrenolicin.[36-42] A route for the synthesis of **12a** starting with 2-bromo-8-methoxy-1,4-naphthoquinone was reported by Kometani et al.[44] The benzindanone **50**, prepared from **49** in three steps, was treated with methylmagnesium iodide and then with HCl to afford the key compound benzindene **51**, which was converted into the conjugated ester **52**. Reduction of **52** with sodium borohydride afforded isomers **53**, which provided a precursor of nanaomycin A (**12a**).

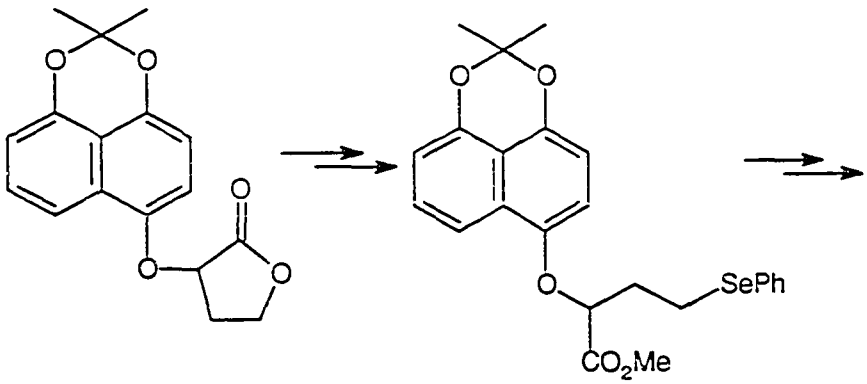


49 50 51

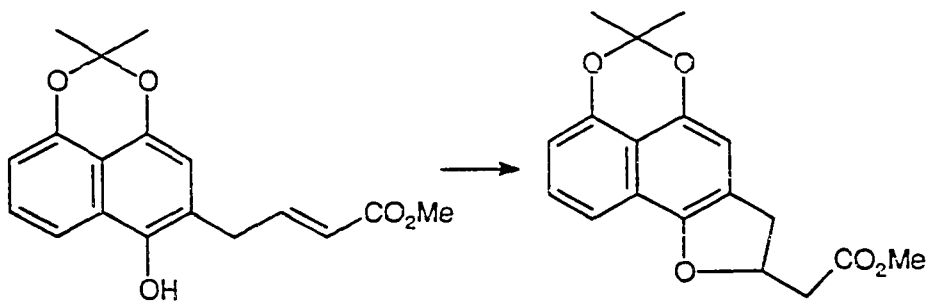


52 53

Another synthetic route to **12a**, involving a new type of Claisen rearrangement, was also developed by Kometani et al.[45] The lactone **54**, prepared in three steps from juglone, was treated with PhSeNa to give phenylselenide **55**. Oxidative elimination of the phenylselseno group gave the alkene which rearranged to naphthylbutenoate **56**. Cyclization of **56** yielded the key dihydrofuran **57**. Oxidative removal of the acetonide of **57** afforded a 2-hydroxybutyrate side chain, which served as the nanaomycin A precursor **58**. From **58**, nanomycin A could be achieved by Li's method.[47]



54 55



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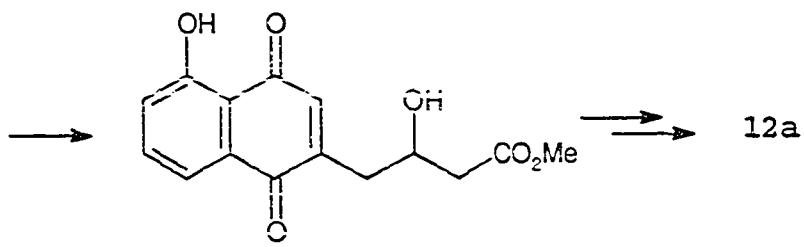
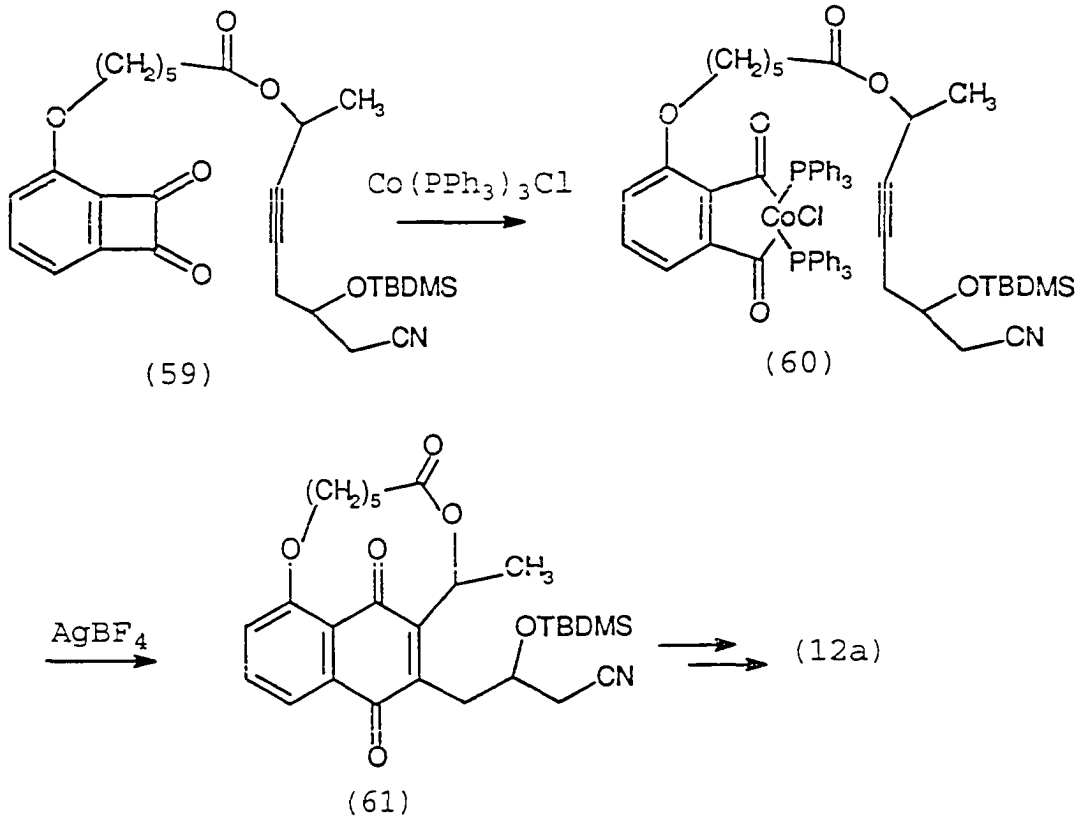


58

An unusual method to prepare the substituted naphthoquinone involving a cobalt complex was developed by South and Liebeskind.[46] Insertion of cobalt into benzocyclobutenedione **59** resulted in the phthaloylcobalt complex **60** which underwent a regiospecific intramolecular

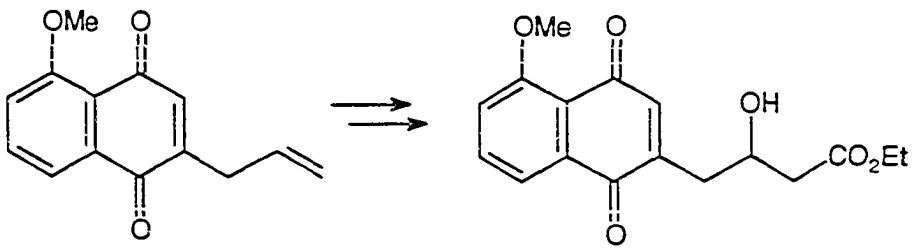


reaction to give a macrocyclic naphthoquinone **61**. Synthesis of nanaomycin A from **61** was accomplished by using a similar method similar to that of Li.[47]

3. Synthesis of kalafungin and related compounds

The first total synthesis of kalafungin was reported by Li and Ellison in 1978.[47] Compound **62**, which was prepared from 2-allyl-5-methoxynaphthoquinone in a multistep sequence, was reduced with zinc and hydrochloric acid followed by treatment with acetaldehyde and silver(I) oxide to afford the

cis-dihydropyran **63**. The cis-dihydropyran **63** was converted to **12a** by demethylation with aluminum chloride, epimerization at C-1 in sulfuric acid, and subsequent hydrolysis. The mixture of kalafungin (**6**) and its enantiomer nanaomycin D (**12d**) was obtained by air oxidation of **12a**.



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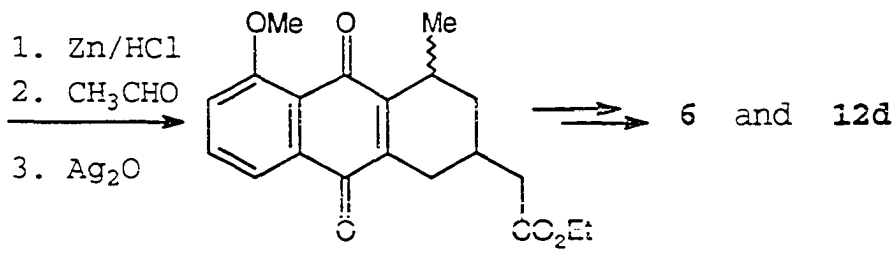
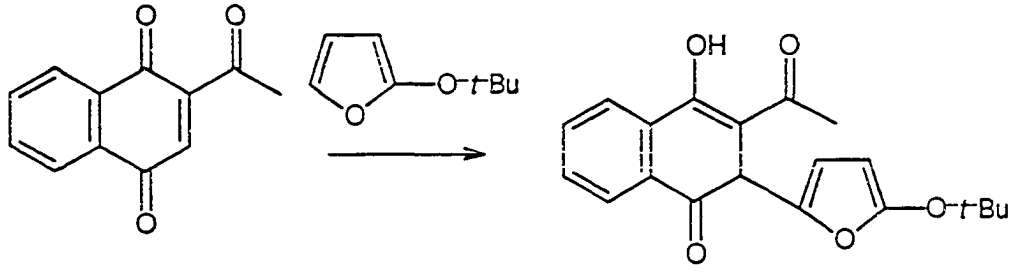


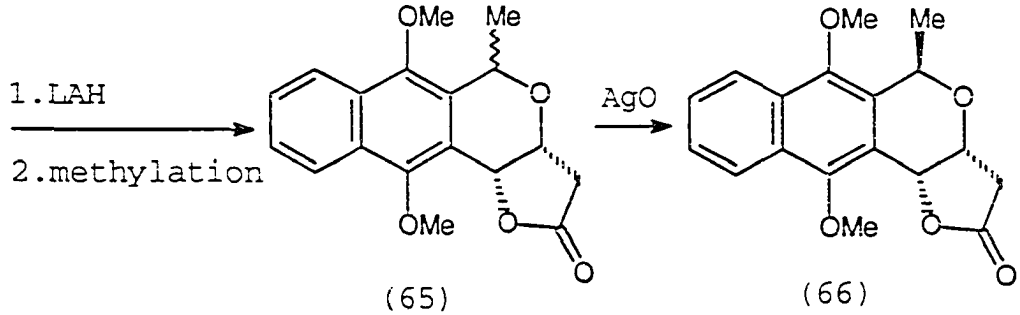
63

At the same time, an efficient synthesis of 9-deoxykalafungin (**66**) in six steps from 2-acetyl-1,4-naphthoquinone was reported by Kraus and Roth.[48] Addition of the 2-*tert*-butoxyfuran to 2-acetyl-1,4-naphthoquinone gave the key intermediate **64** in which all of the carbon atoms present in the target molecular were assembled. Reduction of the ketone with lithium aluminium hydride, followed by removal of

the *tert*-butyl protecting group, afforded compound **65**, which could be oxidized to deoxykalafungin in 17% overall yield.

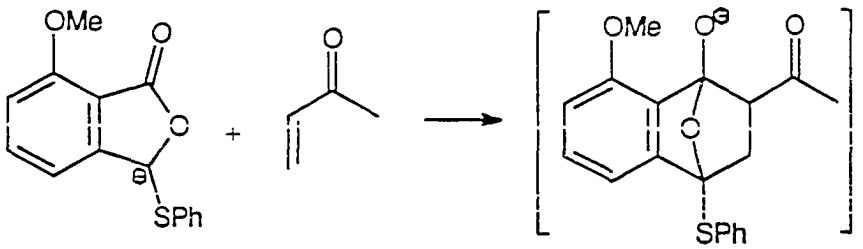


(64)

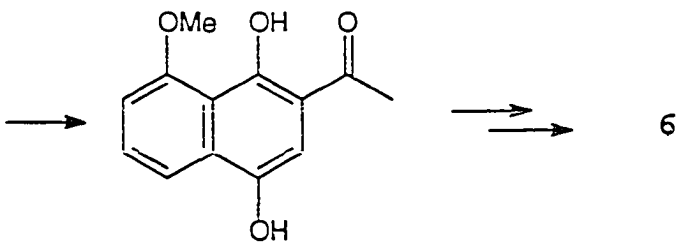


(65) (66)

Kraus et al. also developed a method to prepare functionalized naphthydroquinone by using phthalide annulation.[49] Treatment of anions of 3-(phenylthio)phthalide **67a** with methyl vinyl ketone afforded 2-acetyl-8-methoxy-1,4-dihydroxynaphthalene (**68**). With **68** in hand, a total synthesis of kalafungin was accomplished by using the strategy developed in this lab.[48]

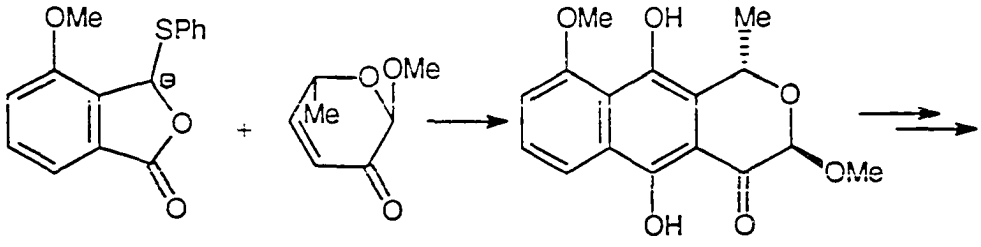


67a

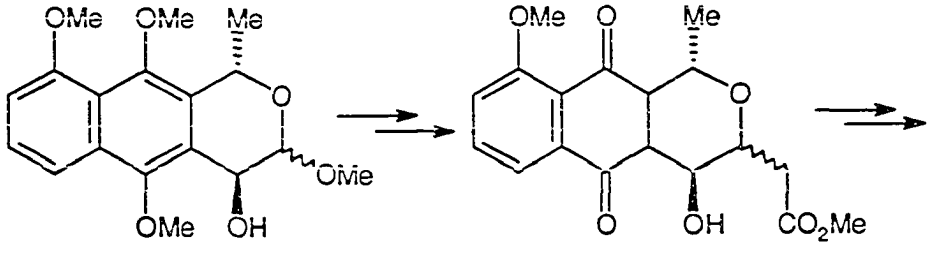


68

Tatsuta and co-workers[50] reported the first enantio-specific total synthesis of kalafungin by using same strategy developed by Kraus.[49] Condensation of anion of 4-methoxy-3-phenylsulfonyl)-1(3H)-isobenzofuranone (**67b**) and optically pure methyl 3,4,6-trideoxy-a-L-glycero-hex-3-enopyranosid-2-ulose (**69**), which was prepared from L-rhamnose by a multi steps, afforded key intermediate **70**. Compound **70** was converted to **71** by several steps. Wittig reaction of **71**, followed by demethylation, epimerization, and lactonization afforded the optically pure kalafungin (**6**).



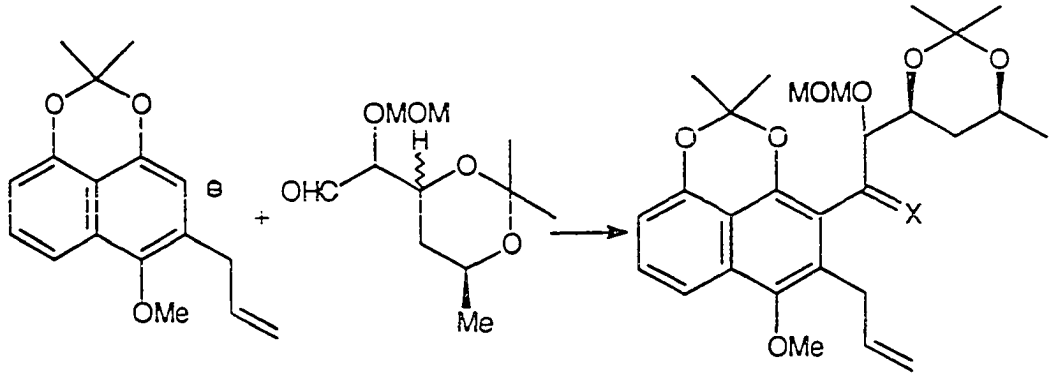
67b **69** **70**



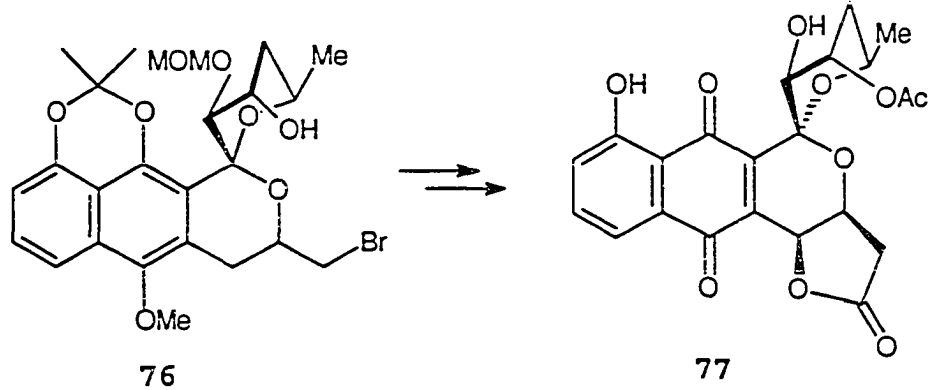
71 **72**

4. Synthesis of (+)-griseusin

The synthesis of griseusin is obviously more difficult than the synthesis of nanaomycins and kalafungin. Yoshi and co-workers reported a total synthesis of (+)-griseusin, an enantiomer of naturally-occurring griseusin A (**14**) in 1983.[51] The properly functionlized naphthalene derivative anion **73** was treated with L-dideoxygulose **74** to provide carbinol **75a**. The ketone **75b** was transformed to bromo spiro ketal **76** by reaction with aqueous N-bromoacetamide and acid-catalyzed intramolecular ketalization. From key compound **76**, (+)-griseusin was obtained by several more steps.



73 74 75a: X=H, OH
75b: X=O

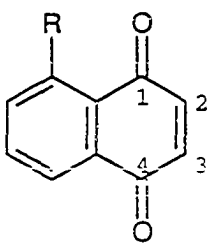


76 77

RESULTS AND DISCUSSION

Synthesis of Pyranonaphthoquinones: The First Approach

In view of the previous work on the synthesis of pyranonaphthoquinone natural products, a common feature is the use of 1,4-naphthoquinone derivatives, including natural product juglone as initial precursors, or preparation of the naphthoquinone skeleton in the first several steps. Various techniques, such as Wittig-Horner olefination, Michael addition, and metal complex coupling reactions have been employed to add side chains in the 2- and 3-position of the naphthoquinone. In most cases, the reaction sequences for



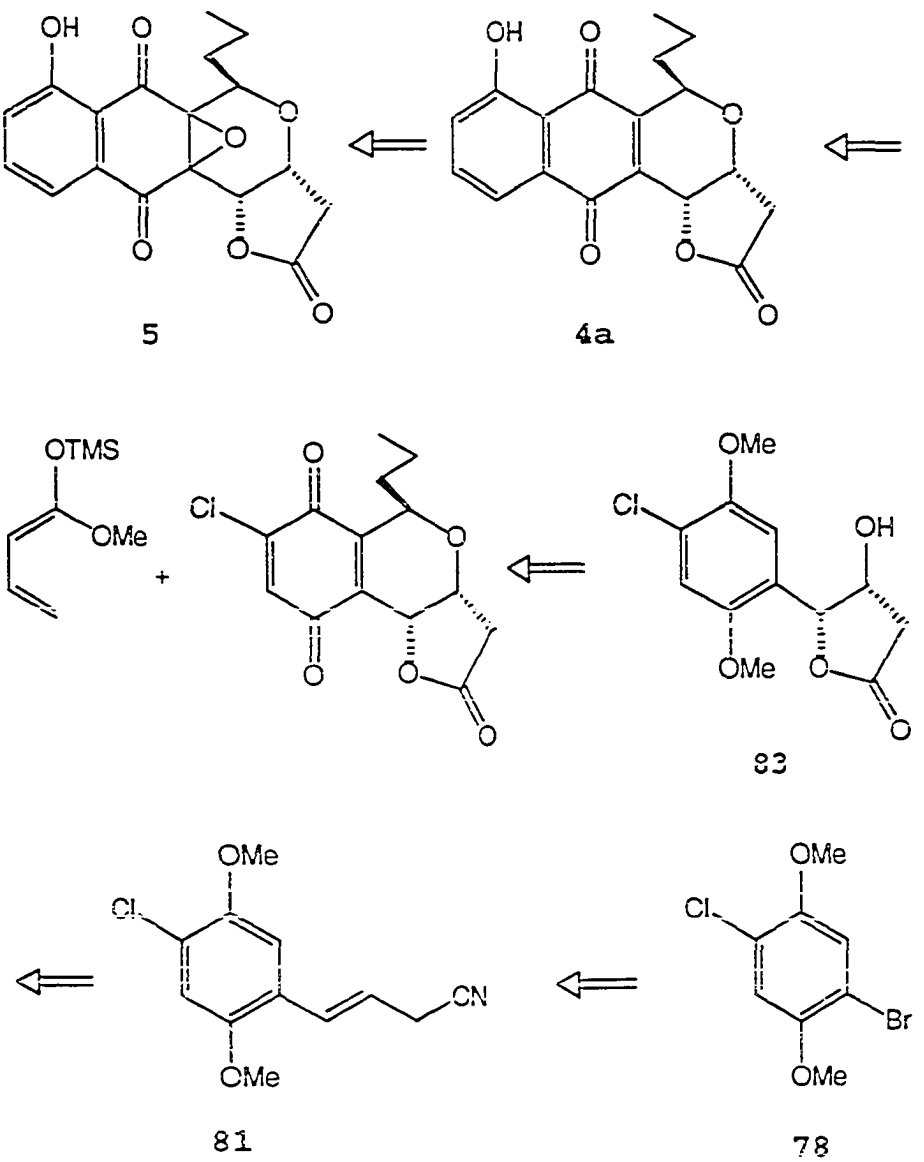
pyran ring construction do not control the stereochemistry of two substituents on the pyran ring, although this is not a serious limitation since equilibration of the side chains occurres in strong sulfuric acid and leds to a mixture rich in the natural trans configuration.[47] While the use of naphthoquinone derivatives as the starting materials is reasonably efficient for the synthesis of relatively simple

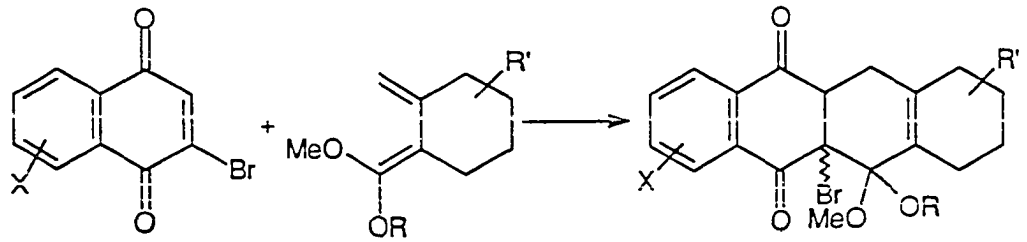
pyranonaphthoquinone natural products, such as nanaomycins, frenolicins, and kalafungin, it is less attractive to use these precursors as the starting materials for the synthesis of more complex compounds, such as SCH 38519 or granaticin. On the other hand, radiolabeled compounds are important in biological tests and metabolic studies. To test the biological activities of pyranonaphthoquinone natural products, scientists usually prefer to radiolabel the naphthoquinone skeleton to monitor their biologically metabolic pathways. In these cases, synthetic routes involving construction of the naphthoquinone skeleton in the last several steps become more attractive for pharmaceutical scientists, and this strategy should also have an potential advantage in the attempt of the synthesis of more complex quinone compounds. Since all of those pyranonaphthoquinone natural products share a common isochromanquinone skeleton, we envisaged a general procedure to prepare these compounds in which the naphthoquinone skeleton could be constructed in the last several steps. Based on this idea, our first approach to these compounds (e.g. frenolicin B) included a regiocontrolled Diels-Alder reaction in the last step of the synthesis. The retrosynthesis is outlined in Scheme 1.

The regiocontrolled Diels-Alder reaction in the last step of our synthesis, first developed by Rapoport et al.,[52] would provide the naphthoquinone skeleton with the necessary

stereochemistry. Dihydroxylation of olefin **81** could generate the asymmetric diol, which would produce an enantioselective approach to our target compound frenolicin B (**4a**) and other

Scheme 1

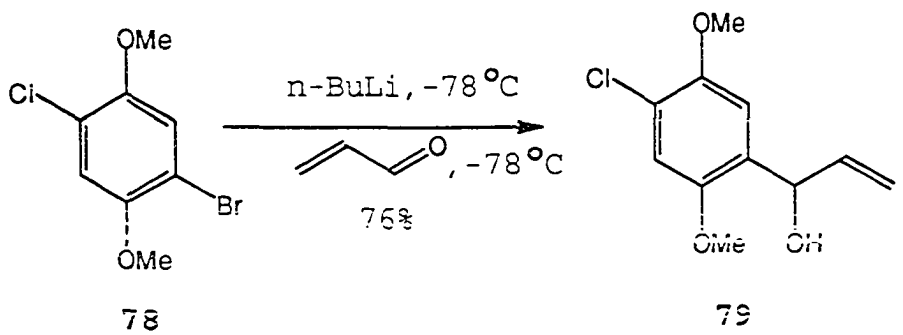




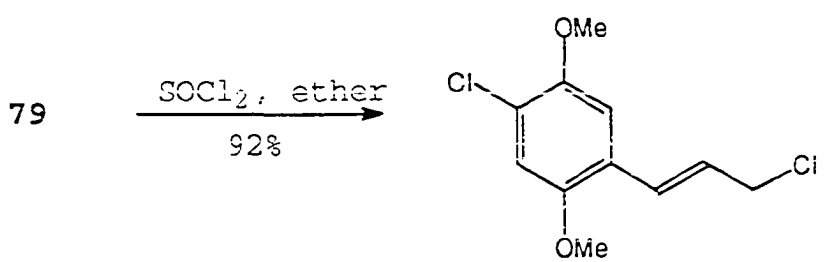
Ref. 52

pyranonaphthoquinone natural products.

To test this approach, the key issue was preparation of the tricyclic moiety. In the course of our investigation, we chose a known compound 2-bromo-5-chloro-1,4-dimethoxybenzene (**78**) as the starting material, which was prepared from



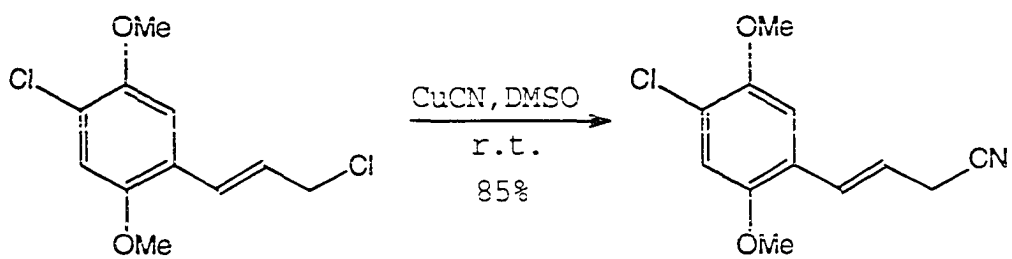
78 **79**



80

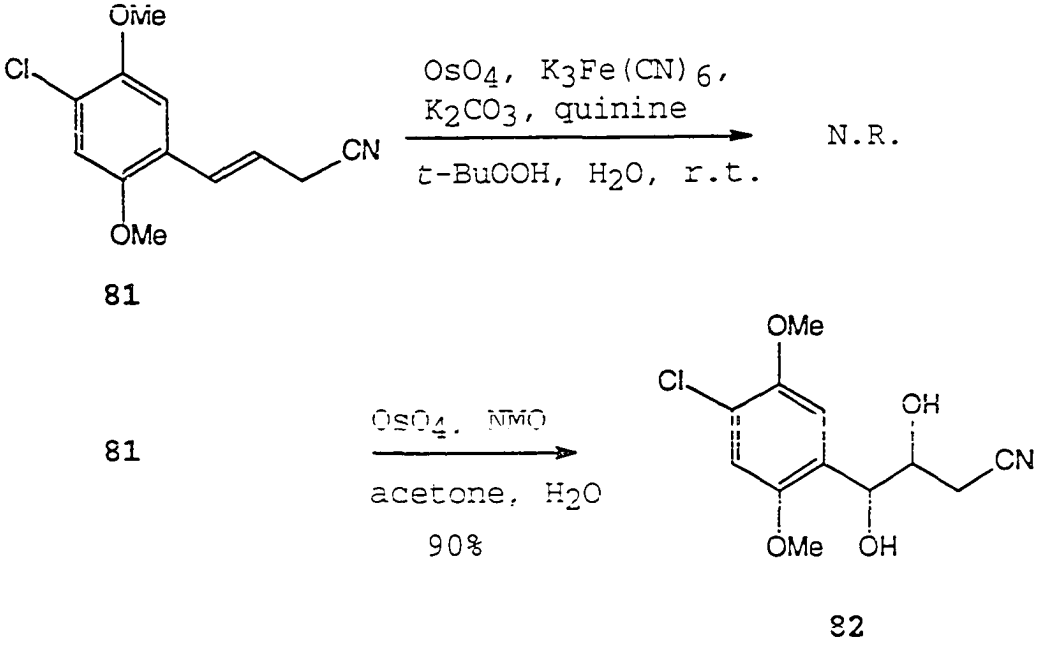
benzoquinone in two steps. Selective metalation of **78** with 1 equivalent of *n*-butyllithium at -78 °C for 30 minutes generated the corresponding anion, which was trapped with acrolein at -78 °C. The resulting solution was stirred at -78 °C for 30 minutes and then warmed to room temperature over 1 hour. The reaction was quenched by saturated ammonium chloride affording allylic alcohol **79** in 76% yield. Allylic chloride **80** was obtained by treatment of the allylic alcohol **79** with thionyl chloride via an S_N2' reaction.

Transformation of allylic chloride **80** to the corresponding allylic cyanide **81** was not as easy as we imagined. Many reaction conditions, such as sodium cyanide/hexane, sodium cyanide/ethanol, sodium cyanide/DMSO, potassium cyanide/DMSO, et al.,[53] were found either to give low yields or to be irreproducible. Finally, we found that the transformation could be achieved by using copper(I) cyanide/dimethyl sulfoxide (CuCN/DMSO). The CuCN/DMSO system proved to be an efficient and reliable method and always gave good yield.



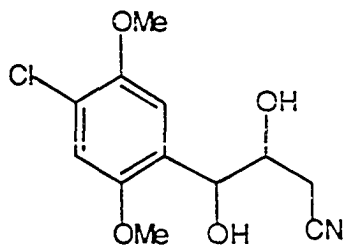
80 **81**

Asymmetric dihydroxylation of allylic cyanide **81** using Sharpless' conditions[54] was found to be sluggish; unreacted starting material **81** was recovered after 7 days at room temperature. An alternative route using a classic catalytic dihydroxylation condition (osmium tetroxide/4-methylmorpholine N-oxide, OsO_4/NMO)[55] afforded the desired racemic diol **82** in 90% yield.



Treatment of diol **82** with *p*-toluenesulfonic acid (PTSA) in THF using Ziegler's method[56] failed to give the desired lactone; only starting material was recovered. Therefore, we had to prepare this lactone by a two steps hydrolysis-lactonization sequence. The nitrile group in molecule **82** was

found unusually stable under normal acid (HCl) and base (NaOH) conditions. Fortunately, sodium peroxide was found to be an effective reagent to hydrolyze this nitrile group.[57] Lactonization of the resulting acid was achieved by using 1,3-dicyclohexylcarbodiimide (DCC) and 4-dimethylamino-pyridine (DMAP)in CH_2Cl_2/THF.



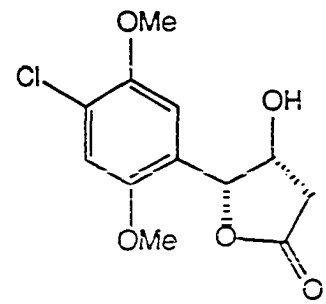
82

PTSA, MeOH
50 °C—reflux

S.M.

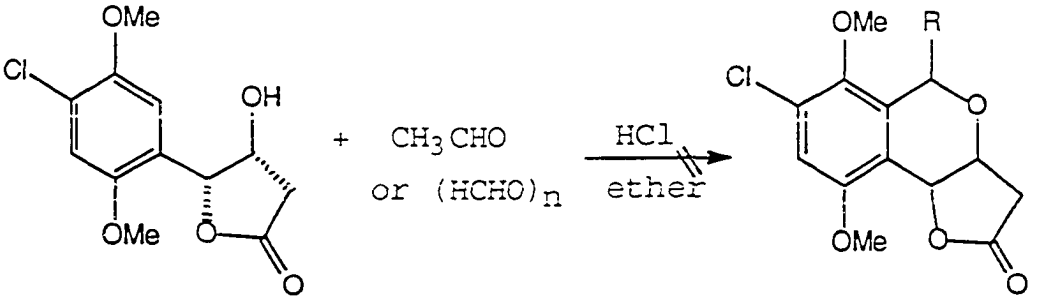
82

1. Na_2O_2/H_2O, 55 °C, 84%
2. DCC, DMAP, CH_2Cl_2
85%



83

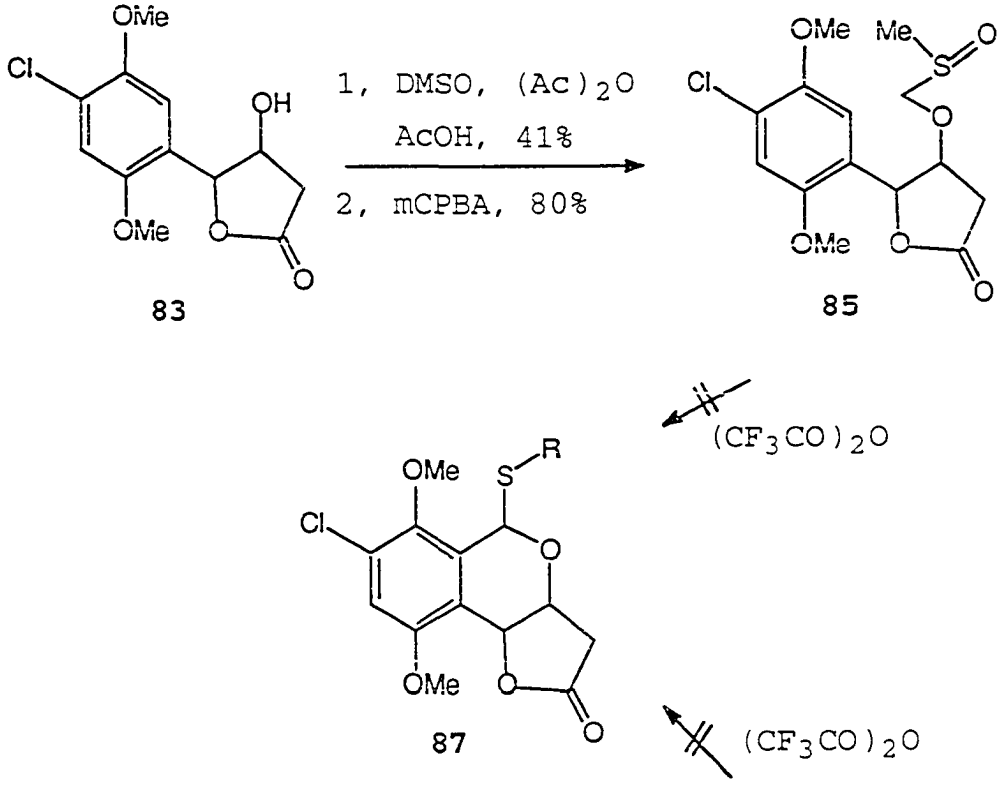
With lactone **83** in hand, we next turned our attention to preparation of the dihydropyran ring. Our first attempt was treatment of the mixture of lactone alcohol **83** and acetaldehyde or formaldehyde with HCl gas at room temperature;[58] unfortunately, these reactions failed to gave any desired products **84**.



83 **84 R=H or Me**

We then tried to make cyclized product **87** by using a Pummerer rearrangement reaction.[59] Treatment of alcohol **83** with DMSO/Ac_2O in glacial acetic acid,[60] followed by oxidation with 3-chloroperoxybenzoic acid (mCPBA),[61] afforded the desired methyl sulfoxide **85**. Unfortunately, compound **85** did not give us any cyclized product under Pummerer reactions condition.[62] We reasoned that the unsuccessful reaction might result from the methyl group of **85** which could be more active than the methylene group in **85** under Pummerer reactions condition. In this case, a phenyl group seemed to be a logical choice to substitute for the methyl group of **85**. To prepare **86**, our first attempt was treatment of the lactone alcohol with $ClCH_2SPh$ using Suzuki's conditions,[63] it is surprising that this reaction gave us only starting material back. Later, a modifieation of Kyler's procedure[64] was found to be successful to prepare the phenyl thioether. Treatment of lactone alcohol **83** with excess methyl phenyl thioether (CH_3SPh) and $(PhCOO)_2$ in acetonitrile, followed by oxidation, afforded the corresponding phenyl sulfoxide **86**. Compound **86**

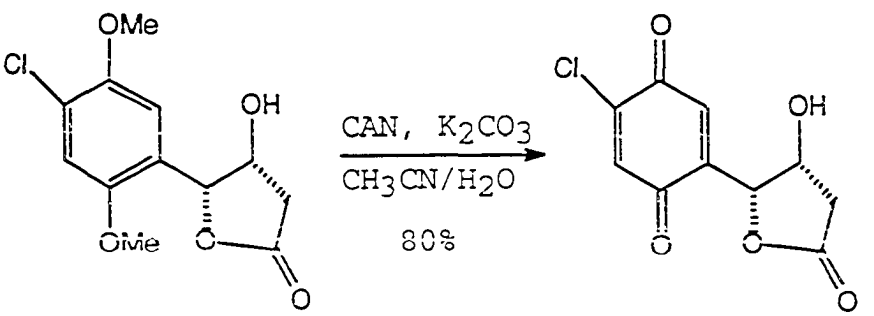
again failed to give the desired cyclization product in trifluoroacetic anhydride.



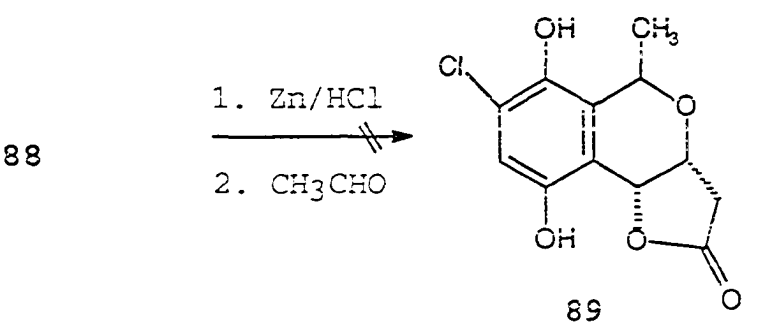
83 85 87 83 86

Attempts to make the pyran ring starting from the corresponding quinone 88 were also tested under several

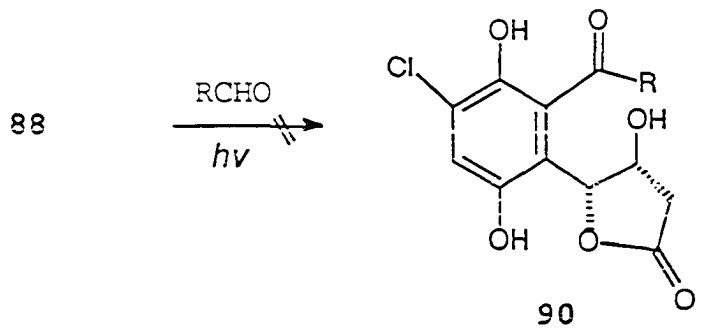
conditions. Reduction of the quinone with zinc and HCl in ethyl ether, followed by treatment of the reaction mixture with acetaldehyde *in situ*,[47] afforded a mess of products. We then turned to a photochemistry approach to generate the other side chain of the quinone **90**. Based on the quinone photochemistry developed by this group,[65] quinone **88** and butyraldehyde were irradiated by a Hanovia lamp; unfortunately, no desired acylhydroquinones were obtained rom these reactions. We reasoned that our system (quinone **88**) was too complex for this photochemical process.



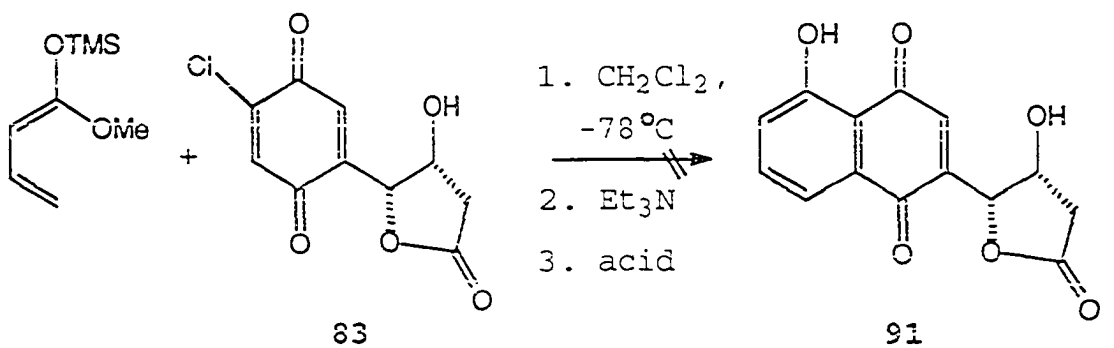
83 **88**



89



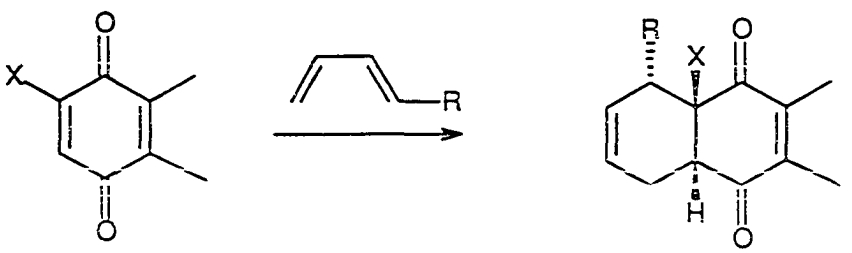
At this stage, we felt that the benzene ring of **83** or quinone **88** might not be electron rich enough to undergo a Friedel-Crafts type reaction since there are a chloro and a lactone attached to the benzene ring, although two electron donating methoxy groups are also on the ring. Therefore, an effort to prepare a naphthoquinone from quinone **88** was also attempted. Treatment of quinone **88** with 1-methoxy-1-trimethylsilyloxy-1,3-butadiene at -78°C, followed by triethylamine afforded only decomposed products.



At this stage, we diverted our research to the second route which is described in the next section.

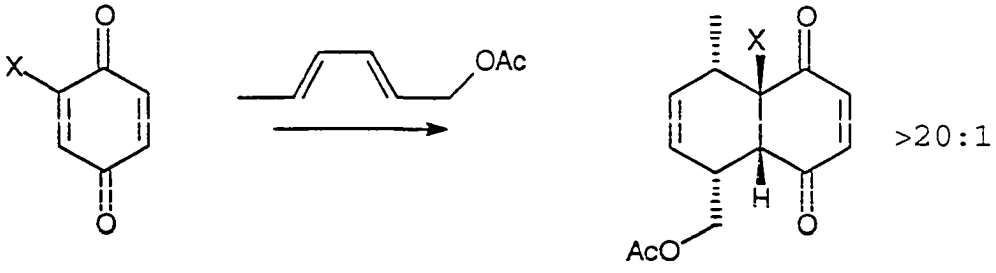
Synthesis of Pyranonaphthoquinones: The Second Approach

Regiospecific cycloaddition reactions are widely used in the syntheses of quinone natural products.[66] Among the pathways featuring a cycloaddition reaction, one of the most general methods for the regiospecific synthesis of substituted quinones was pioneered by Rapoport and co-workers.[52] This method involves the Diels-Alder reaction of a substituted quinone and is depicted below. The X group is usually chlorine or bromine, but sulfoxides and nitriles can also be employed.[67] However, the necessity of the X group often simply refocusses the synthetic problem to a regioselective synthesis of the substituted quinone.



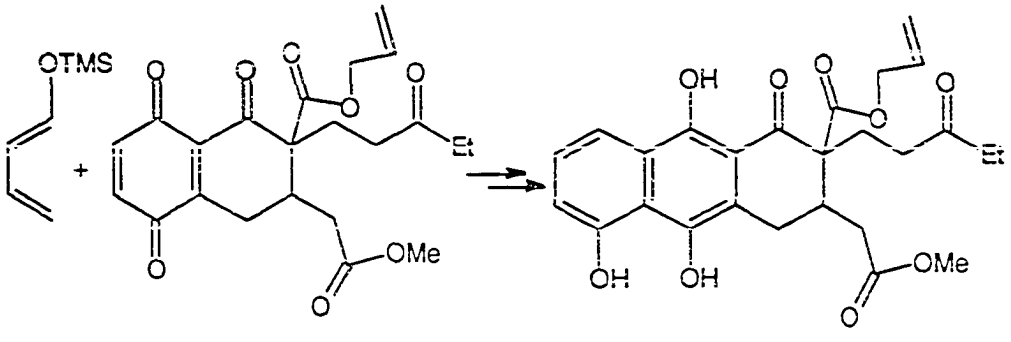
Ref. 52

Our group has been interested in evaluating the directing effects of functional groups not directly attached to the atoms involved in the cycloaddition reaction. Kraus et al. discovered a highly regioselective Diels-Alder



Ref. 68

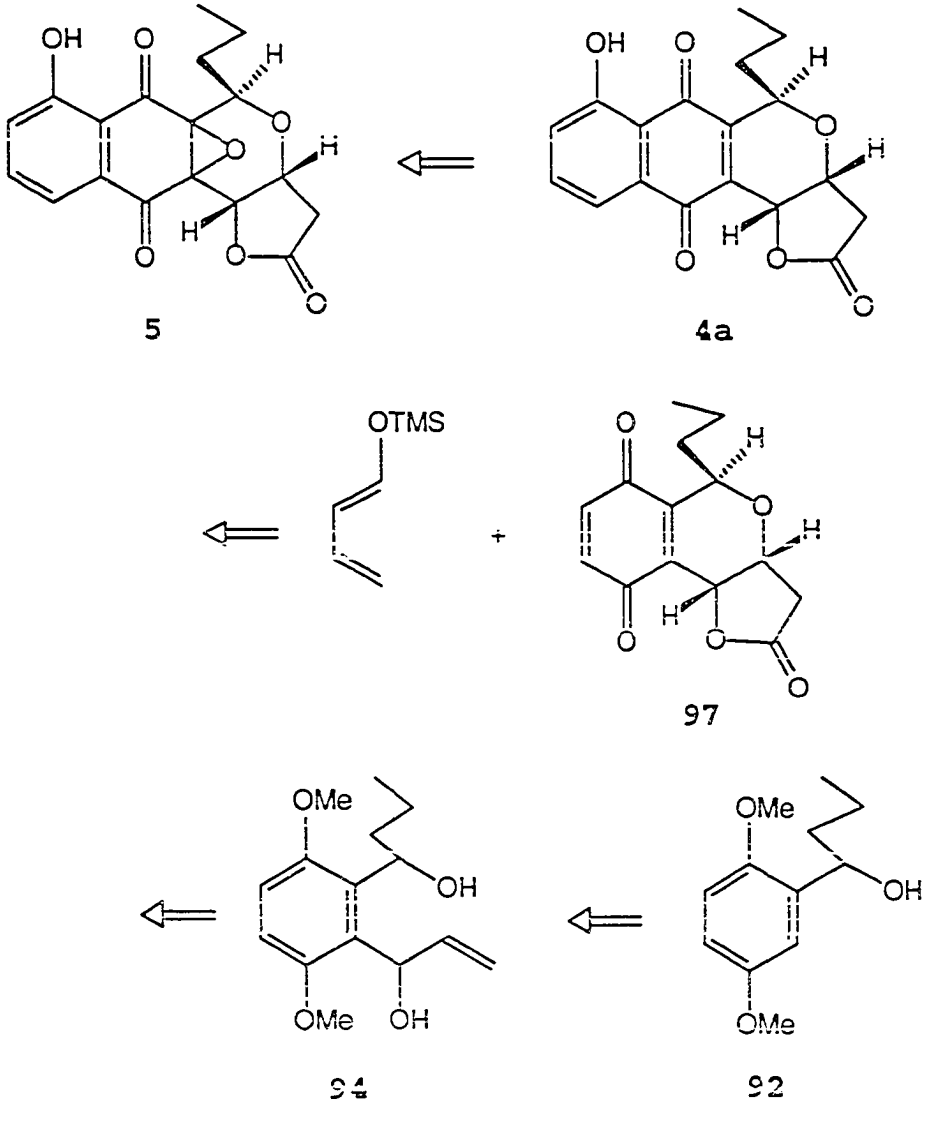
reaction.[68] The allylic ester moiety on the diene appears to be responsible for controlling the excellent regioselectivity, since the corresponding alcohol or methyl ether furnished essentially a 1:1 mixture of regioisomeric adducts. Kraus and Chen also demonstrated another example of the regioselectivity of cycloaddition in their synthesis of 7-deoxyaklavinone in 1991.[69] Although the details of the regioselectivity of the cycloaddition were not very clear at that time, we believed that the electron withdrawing ketone group attached to the quinone could play a key role to control the selectivity.



Ref. 69

Our previous study indicated that the lactone attached to the quinone **83** might be an electron-withdrawing group, since the lactone inhibited the Friedel-Crafts type reactions in compound **83**. Thus, the lactone could be a possible group

Scheme 2



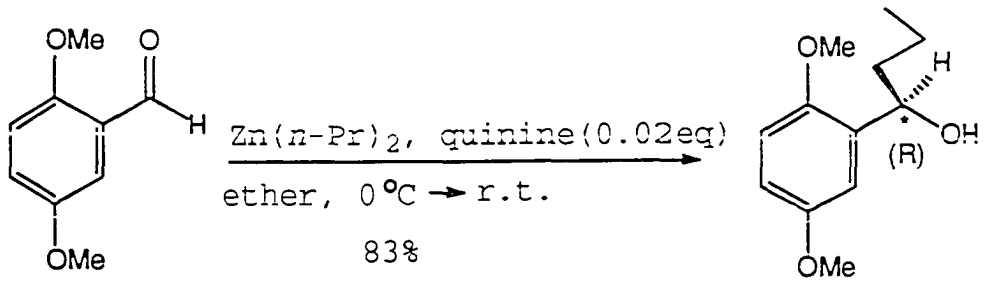
5 **4a** **97** 94 92

to control the regioselectivity of the cycloaddition. In this case, the directing group X attached to the dienophile might not be necessary and could be removed from the synthetic design to simplify the synthetic route. Based on this idea, we designed our second approach to the frenolicin B and its analogs which was outlined in Scheme 2.

The key reaction was a Diels-Alder reaction which constructs the naphthoquinone in the last step. The regioselectivity of cycloaddition could be controlled by a remote substituent, such as a lactone. Asymmetric alcohol **92** could induce an enantioselective total synthesis of frenolicin B and its analogs.

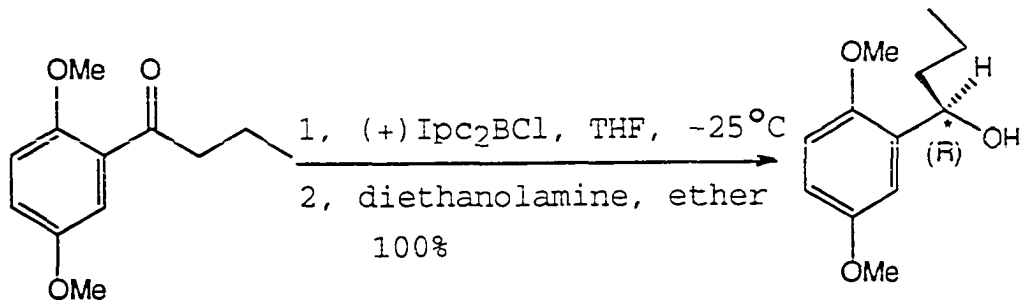
1. The enantioselective synthesis of frenolicin B and α, β-epoxyfrenolicin B

The first step of our synthesis was preparation of asymmetric alcohol **92**. The reduction of 2,5-dimethoxy-butyrophenone[70] using (+)-Ipc_2BCl according to the method of Brown afforded alcohol **92** in 100% yield.[71] Proton NMR analysis of the Mosher ester[72] of **92** indicated an enantiomeric excess of approximately 95%. This reaction was superior to the reaction of 2,5-dimethoxybenzaldehyde with di-*n*-propylzinc[73] and quinine which proceeded in 83% yield and afforded an enantiomeric excess of only 70%.[74]



92

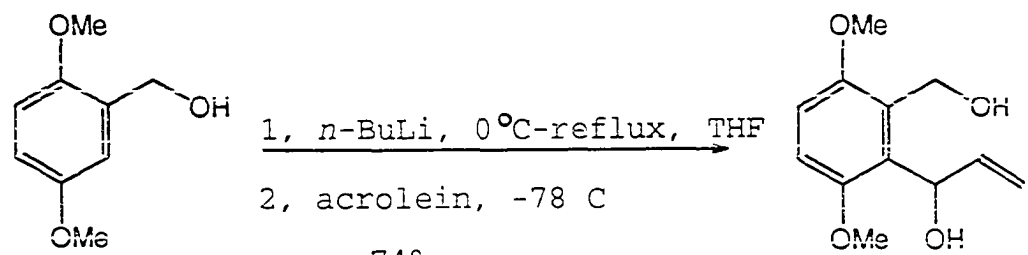
70% e.e.



92

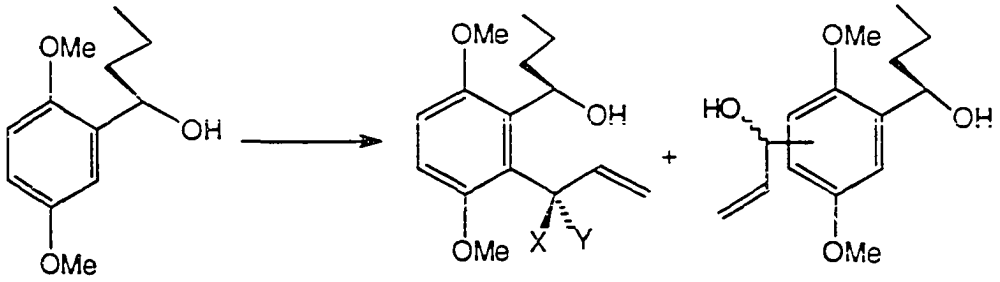
93-95% e.e.

The metalation of 2,5-dimethoxybenzyl alcohol using two equivalents of *n*-butyllithium in THF to generate a dianion, followed by reaction with acrolein, afforded diol **93** in good yield (70%) and high selectivity. When the same reaction



93

conditions were conducted with alcohol **92**, it gave a poor result and diols **94a** and **94b** were obtained in a combined yield of only 22%. The major products appeared to be derived from metalation either meta or para to the benzylic alcohol. Several different solvent systems were tested in this reaction and the results are listed below. From these results, we found that the more polar solvent we used, the less desired ortho-product we got. A coordinating reagent, such as N,N,N',N'-tetramethylethylene-diamine (TMEDA), did not provide more ortho-products.[75] Instead, more para products were obtained when TMEDA were used. Obviously, the polarity of the solvent system played a key rule in the selectivity of the metalation. Thus, control of the metalation selectivity for our benzylic alcohol could be achieved simply by decreasing the polarity of the solvent. This might be a generally useful method, but limited by solubility of the dianion. In a related synthesis of hongconin,[76] increasing the proportion of pentane in the ether:pentane solvent mixture also improved the yield of ortho-metallated products. When the reaction was conducted in a 1:10 ether:pentane solution, the alcohols **94a** and **94b** were isolated in 56% yield, with only 10% of the undesired isomeric product. Diols **94a** and **94b** were generated in a 1.5:1 ratio and could be separated by flash chromatography and recrystallization. In this case, the effectiveness



92

94a: X=H, Y=OH

94b: X=OH, Y=H

92 $\xrightarrow[\text{2. acrolein, } -78\,^{\circ}\text{C, 51\%}]{\text{1. } n\text{-BuLi, THF, } 0\,^{\circ}\text{C-reflux}}$ 3 : 4

92 $\xrightarrow[\text{2. acrolein, } -78\,^{\circ}\text{C, 58\%}]{\text{1. } n\text{-BuLi, THF, } 0\,^{\circ}\text{C-reflux, TMEDA}}$ 1 : 10

92 $\xrightarrow[\text{2. acrolein, } -78\,^{\circ}\text{C, low yield}]{\text{1. } n\text{-BuLi, hexane, } 0\,^{\circ}\text{C-reflux, TMEDA}}$ 1 : 4

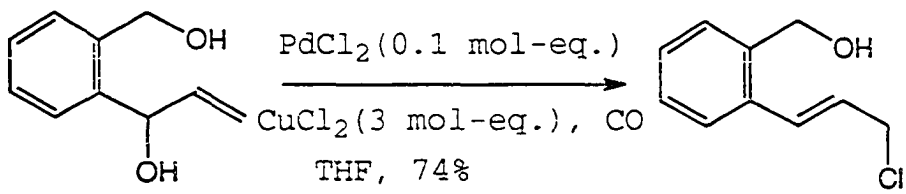
92 $\xrightarrow[\text{2. acrolein, } -78\,^{\circ}\text{C, 61\%}]{\text{1. } n\text{-BuLi, ether, } 0\,^{\circ}\text{C-rt}}$ 2.5 : 1

92 $\xrightarrow[\text{2. acrolein, } -78\,^{\circ}\text{C, 67\%}]{\text{1. } n\text{-BuLi, ether:pentane=1:10, } 0\,^{\circ}\text{C-rt}}$ 5 : 1

(**94a/94b**=1.5/1)

was limited by the solubility of the anion of the benzylic alcohol.

Our attention next turned to the synthesis of the tricyclic compound **95**. Although Semmelhack et al.[77] reported a palladium-based method to prepare compounds similar to **95**, some problems still needed to be solved. In their research, Semmelhack et al. found that the cyclization of alcohol **96** under the standard catalytic alkoxycarbonylation conditions (0.1 mol of $PdCl_2$, 3.0 mol of $CuCl_2$, CO at 1.1 atm) gave only rearranged product **97**. The desired cyclization was

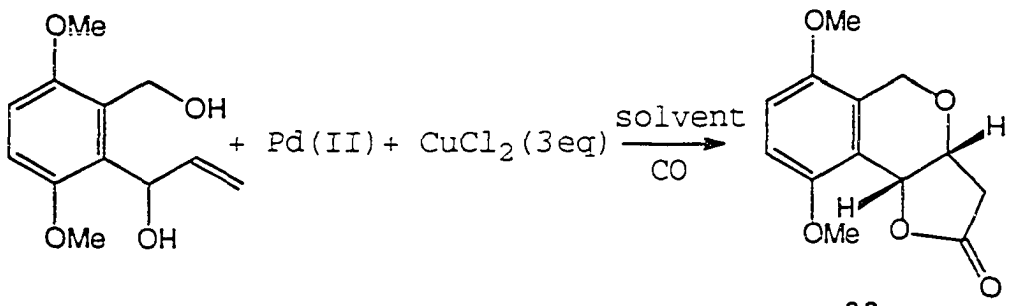


96 **97**

Ref. 61

achieved only when stoichiometric amounts of of palladium diacetate (1.0 mol) were used in the reaction. In our research, we hoped to perform this reaction by using catalytic amounts of palladium to achieve an efficient and economical synthesis. Therefore, a series of reaction conditions were tested on readily available diol **93** under catalytic conditions (5% mol Pd(II), 3 mol $CuCl_2$, CO at

Table 1. Optimization of the Pd(II)-catalyzed cyclization of diol **93**

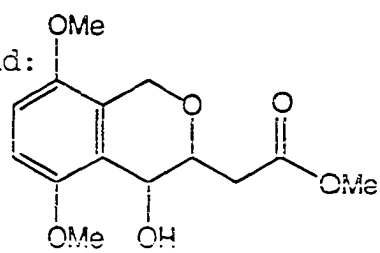


93 **98**

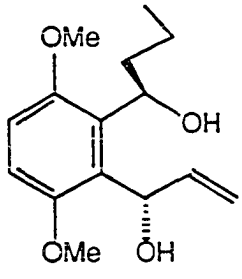
5% Pd(II)	solvent	**98** yield(%)
$PdCl_2$	DMF	18
$Pd(OAc)_2$	DMF	33
$Pd(OAc)_2$	THF	30
* $Pd(OAc)_2$/base	THF	15-31
$PdCl_2(CH_3CN)_2$	DMF	20
$PdCl_2(CH_3CN)_2$	THF	23
$PdCl_2(CH_3CN)_2$	DMSO	20
$PdCl_2(CH_3CN)_2$	CH_3CN	16
** $PdCl_2(CH_3CN)_2$	CH_3OH	12

*basic compounds including pyridine, Et_3N, Na_2CO_3, KOAc, BaO etc.

**another product was also found:

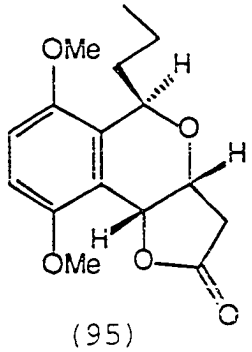


1atm). Different palladium compounds were found to give the same cyclized products and produced no major differences in yields (yields ranged from 15% to 30%). Interestingly, catalytic $PdCl_2$ (5% mol) in our system also gave the desired tricyclic product **98**. Solvents such as DMF and DMSO, which could improve the solubility of $CuCl_2$ and Pd(II) reagents did not show any advantage over conventional solvents, such as THF. Many bases, including inorganic bases (Na_2CO_3, KOAc, BaO, etc.) and organic bases (pyridine, triethylamine) also had no obvious effect on improving the yields. In this



(94a)

5% $Pd(OAc)_2$
$CuCl_2$(3eq.)
CO, THF
20-35%



(95)

(94a)

30% $Pd(OAc)_2$
$CuCl_2$(3eq.)
CO, THF
61%

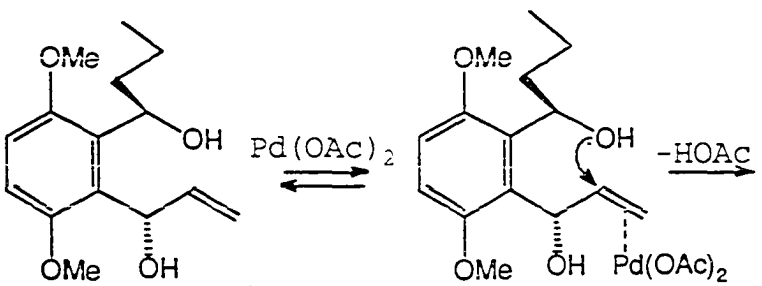
(95)

(94a)

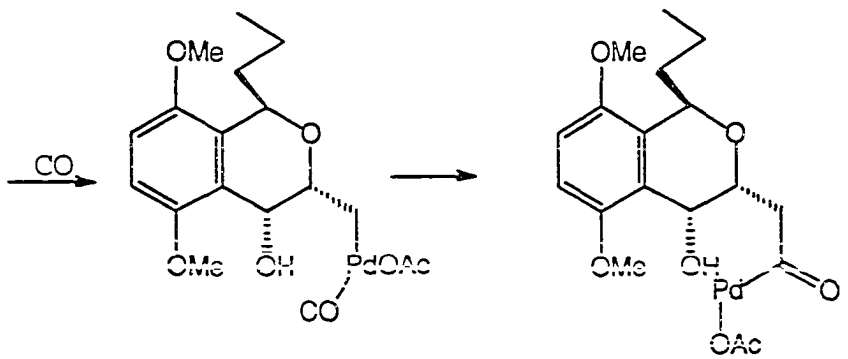
$Pd(OAc)_2$(1eq.)
$CuCl_2$(3eq.)
CO, THF
65%

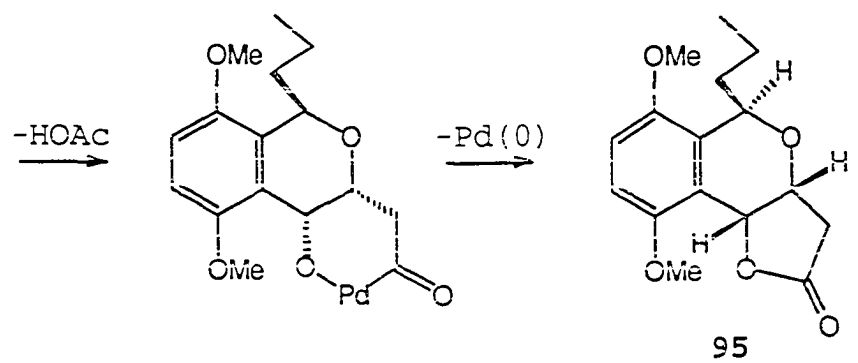
(95)

case, an economical and easy handling system ($Pd(OAc)_2$, $CuCl_2$, THF, CO) was chosen for further study. Later, cyclization of diol **94a** with 30% mol of $Pd(OAc)_2$ was found to give desired lactone **95** in 61% yield, which was comparable to stoichmetric condition's result (65% yield). Here, control



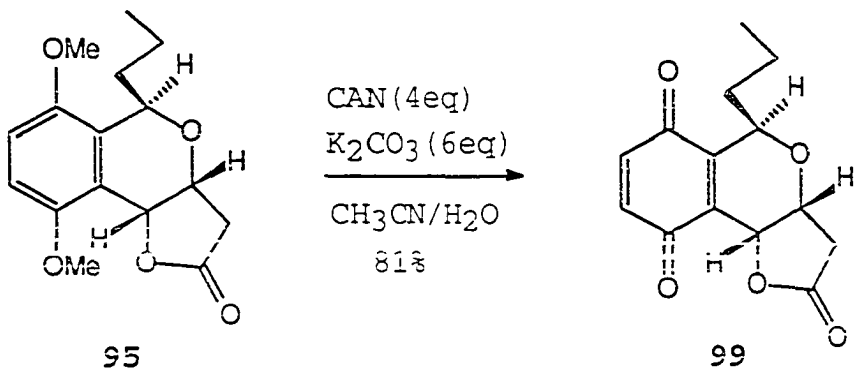
94a



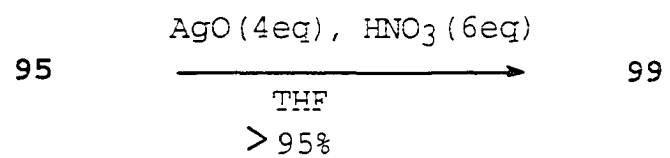


95

of concentration (<0.05 mmol/ml) of diol was found to be crucial for the success of this reaction. Although 30% Pd(II) was consumed in this reaction, we are still satisfied with the result, since several steps were involved in this one pot reaction (see above). Semmelhack et al. found that cyclization of a diol afforded a mixture of lactones.[77] Fortunately, cyclization of diol **94a** under our conditions gave only desired product **95**. The oxidation of lactone **95** with ceric ammonium nitrate (CAN) provided **99** in 80% yield. An alternative method using AgO[78] gave much better results. (95% yield).



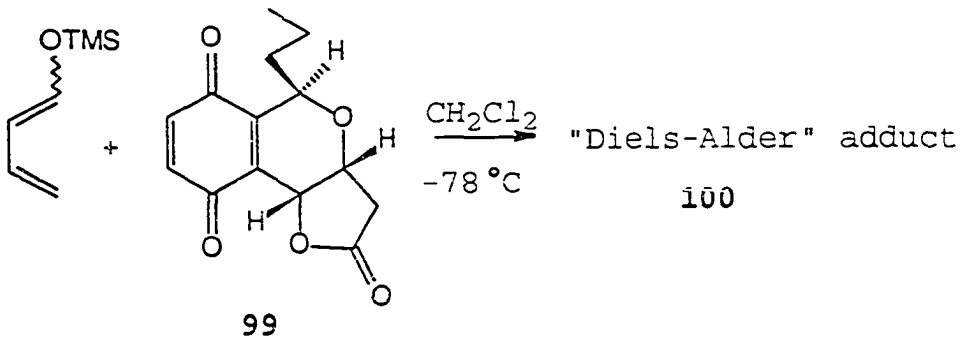
95 **99**

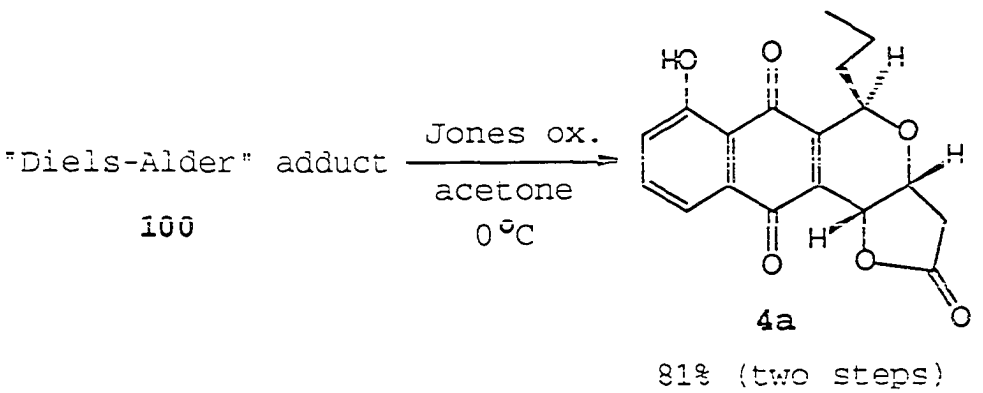


95 **99**

In order to determine whether the lactone moiety could influence the regioselectivity of the Diels-Alder reaction,

we examined a Diels-Alder reaction of quinone **99**. Treatment of benzoquinone **99** with 1-trimethylsilyloxy-1,3-butadiene afforded a Diels-Alder adduct which was immediately treated with excess Jones reagent to provide frenolicin B (**4a**) in 81% isolated yield from **99**. There were no traces of an isomeric quinone. Our product was identical by proton NMR, IR, TLC and ^{13}C NMR to an authentic sample of frenolicin B supplied by the Hoffmann-LaRoche company. In order to be absolutely

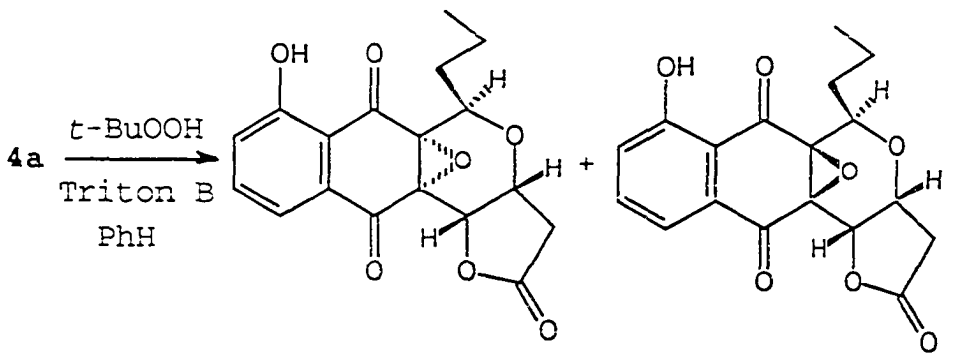




certain that the regioselective reaction actually generated the desired product, we also determined the structure of our compound by X-ray crystallography.[79]

The synthesis of α, β-epoxyfrenolicin B was achieved by epoxidation of frenolicin B with *tert*-butyl hydroperoxide and Triton B in benzene in excellent yield. The ratio of α- and β-epoxyfrenolicin B depended on the reaction temperature. The results are shown in Table 2.

Table 2. Synthesis of α- and β-epoxyfrenolicin B from frenolicin B: temperature effect



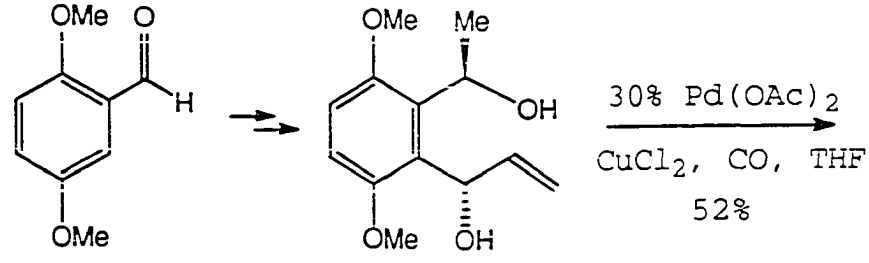
101a **101b**

α-Epoxyfrenolicin B β-Epoxyfrenolicin B

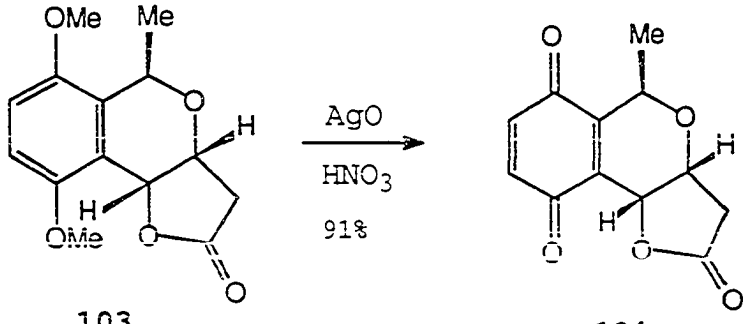
Reaction Temperature(°C)	Yield(%)	Ratio **101a:101b**
25	91	8:1
50	88	5:1
80	86	3:1

2. The synthesis of racemic kalafungin

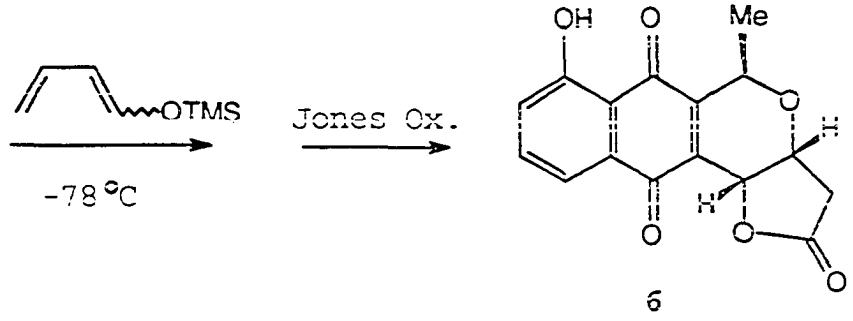
Kalafungin (6) is a novel antifungal agent. Kalafungin has been synthesized by Li, Kraus and by Tatsuta.[47-50] We were interested in extending the strategy developed in the



102



103 104

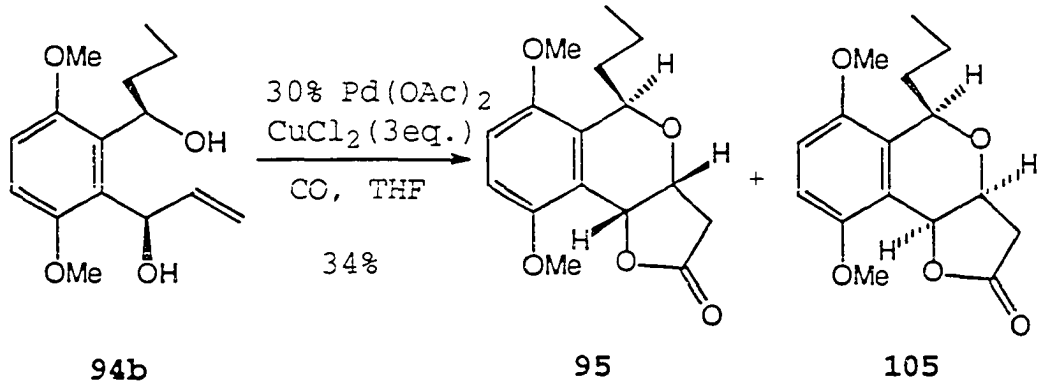


6

63% from 104

frenolicin B synthesis to a direct synthesis of kalafungin. Our synthesis of racemic kalafungin (**6**) began with diol **102**, a key intermediate in our synthesis of hongconin.[6] The reaction of **102** with 30% mol palladium acetate and cupric chloride under an atmosphere of carbon monoxide provided lactone **103** in 51% yield. Oxidation using the standard Rapoport conditions (AgO, HNO_3) generated benzoquinone **104** in 91% yield. Quinone **104** was treated with 1-trimethylsilyloxy-1,3-butadiene in methylene chloride, followed by Jones oxidation, to provide racemic kalafungin (**6**) in 63% yield from **104**. Our spectra of racemic kalafungin were identical to those of a sample synthesized by our group using a completely different synthetic route.[49]

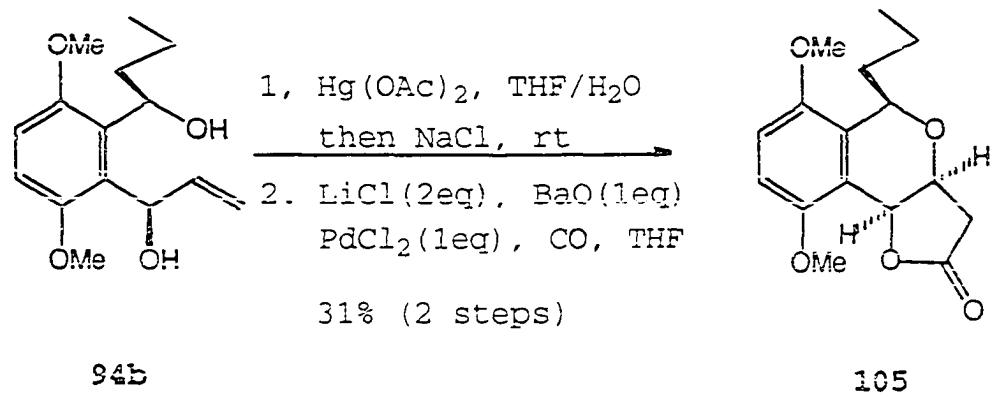
The excellent regioselectivity was welcome but was not expected. In order to better understand the origins of the selectivity in terms of the structure of the quinone, we prepared the isomeric quinone **106**. This molecule was synthesized to probe the steric effect of the propyl group. Isomeric diol **94b** was first used as a starting material to prepare **106**. When the same catalytic alkoxycarbonylation conditions (30% mol $Pd(OAc)_2$, 3 mol $CuCl_2$, CO at 1 atm) were conducted on **94b**, two inseparable tricyclic compounds **95** and **105** were obtained in a 2:5 ratio. This forced us to develop two reaction sequences to prepare pure **105**.



94b **95** **105**

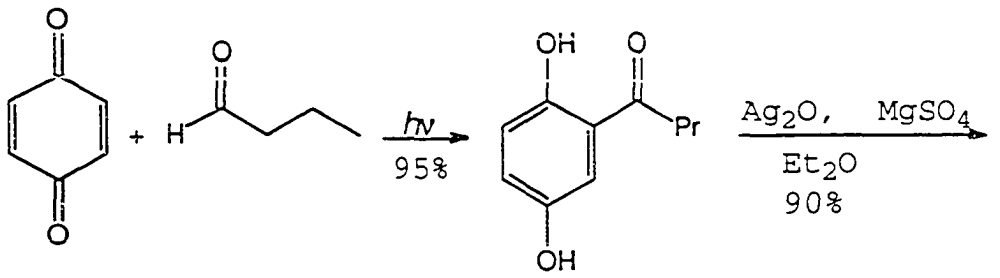
95 : 105 = 2:5

Treatment of **94b** with mercuric acetate in aqueous THF, followed by sodium chloride, generated the pyran according to the method of Maruyama.[80] The resulting mercurial reacted with palladium chloride, lithium chloride, barium oxide, and carbon monoxide (1 atm) in THF according to the method of Larock[81] to give **105** in 31% yield over two steps. Oxidation of **105** by AgO and HNO_3 afforded quinone **106**.



94b **105**

An alternative route of preparation of quinone **106** was based on photochemistry/Michael addition reactions. Irradiation of benzoquinone and butyraldehyde in benzene gave 1-(2,5-dihydroxyphenyl)-1-butanone (**107**) in high yield (95%) according to the method of Kraus.[65] Oxidation of **107** with Ag_2O, followed by treatment of quinone ketone **108** with 2-



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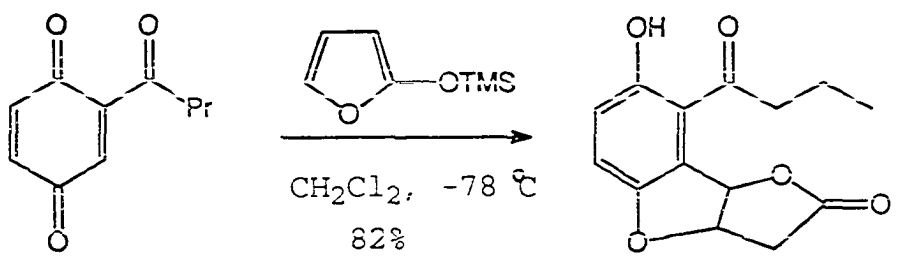
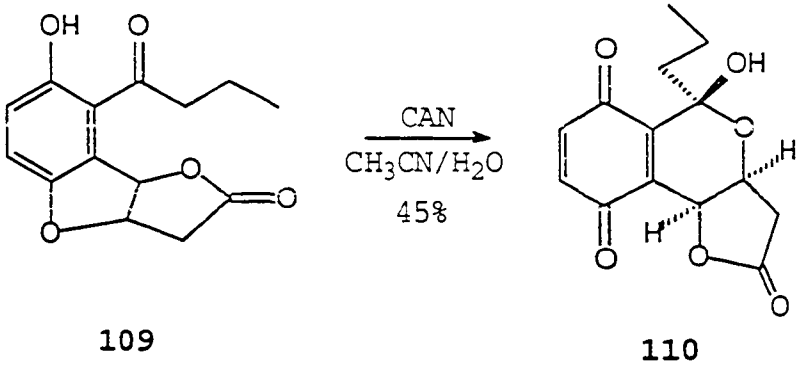
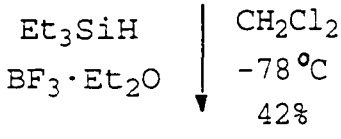


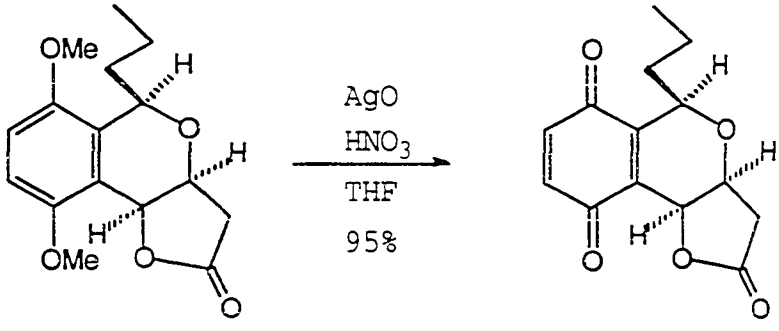
108 **109**

(trimethylsilyloxy)-furan according to the method of Kraus and Shi,[82] provided compound **109**. Treatment of **109** with ceric ammonium nitrate in aqueous acetonitrile generated cyclized compound **110**. Dehydroxylation of **110** with BF_3-



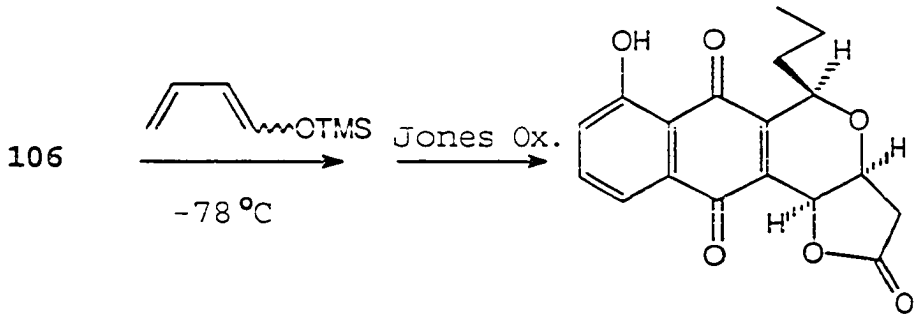
109 **110**





105 **106**

Et_2O and Et_3SiH in methylene chloride[42] gave quinone **106**, which was identical with that obtained by oxidation of **105**. The reaction of **106** with 1-trimethylsilyloxy-1,3-butadiene followed by Jones oxidation of the unpurified adduct afforded 5-epi-frenolicin B (**4b**)in 65% yield. Thus, the regioselectivity of the Diels-Alder reaction was excellent in cycloadditions both with quinones bearing an exo propyl group and with quinones bearing an endo propyl group.



4b

Molecular Electrostatic Potentials-A Rationale for Regioselectivity*

In order to better understand the role of the ring substituents on the regioselectivity of the Diels-Alder reaction discussed above, the molecular geometries of **99** and **106** were optimized without symmetry constraints at the AM1[83] level of theory and verified as minima by calculating numerically and then diagonalizing the Hessian (matrix of energy second derivatives). Although the initial optimizations resulted in structures in which the propyl group on the dihydropyran ring is equatorial (hereafter referred to as **99e** and **106e**), subsequent studies indicated that the conformations with axial propyl groups (**99a** and **106a**) are slightly lower in energy. At the AM1 level of theory, the free energy at -78°C (ΔG_{195}) for **99e** and **106e** is

* Caculation was done by Dr. Mark Gordon and Jan H. Jensen

2.7 (1.9) kcal/mol higher than **99a** and **106a**. Single point RHF/6-31G(d)[84] energy calculations using the AM1 geometries and frequencies (denoted RHF/6-31G(d)//AM1) resulted in very similar ΔG_{195}'s: 2.4 kcal/mol for **99** and and 3.0 kcal/mol for **106**. The conclusions drawn regarding the observed regioselectivity are independent of whether the propyl group is axial or equatorial, as will be shown below.

The RHF/6-31G(d) function waves were then used to calculate molecular electrostatic potentials (MEPs).[85] Here, an MEP is defined as the potential felt by a +1 test charge due to the molecular charge density, evaluated over a grid of points in a given plane of the molecule. The contour map thus generated identifies relative positively and negatively charged regions of the molecule and can be used, for example, to indicate likely sites for electrophilic and nucleophilic attack. All calculations were performed with the electronic structure program GAMESS.[86]

Figure 1 shows two MEPs of **99a** evaluated in planes 2 Å below (Figure 1a) and 2 Å above (Figure 1c) and parallel with the dienophile (DP) plane. Figure 1b schematically depicts the orientation of **99a** in the MEPs. Both MEPs show a positive center region (solid lines) with negative regions (dotted lines) at either side. The plane above the ring shows an almost equal negative charge distribution on either side. The plane below the ring shows more negative charge on

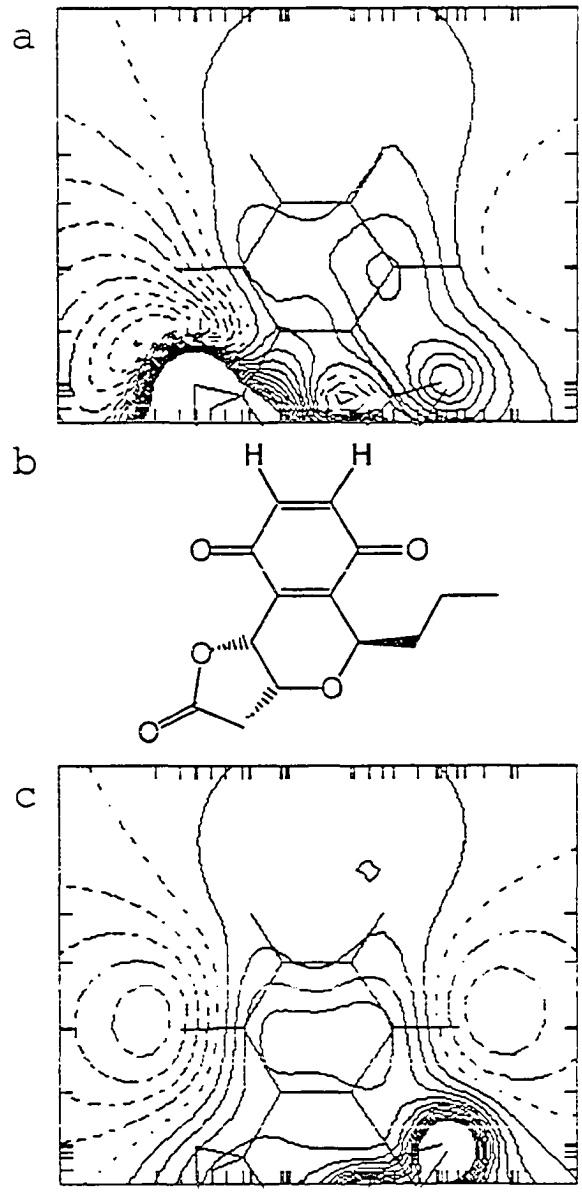


Figure 1 MEPs of **99a** evaluated in planes 2 Å below (a) and above (c) the DP plane. The contour spacing is 5 kcal/mol•e. (b) schematic orientation of **99a** in the MEPs

the left side, presumably due mostly to the lactone ringoxygen, and only one negative contour on the right side.

Compare this to the MEP of the diene 2 Å above the s_v symmetry plane, shown in Figure 2. The MEP shows significantly more negative charge on the substituent side of the diene, presumably due to an oxygen lone pair, in the region most likely to interact with dienophile substituents (see Figure 2c and the MEPs in Figure 1). This assumes the TMS group is *cis* to the neighboring CC double bond, which is the orientation that minimizes steric interactions of the bulky TMS as the diene and dienophile approach. Thus, the MEPs in Figures 1 and 2 indicate that the incoming diene should prefer to react with **99** from below the plane of the ring with the OTMS substituent away from the butyrolactone ring. The other three approaches are disfavored by electrostatic repulsions between the OTMS substituent and the butyrolactone ring and quinone oxygens, as depicted schematically in Figure 3. This provides a rationale for the experimentally observed regioselectivity, and the Diels-Alder adduct **100** is predicted as a synthetic intermediate between **99** and **4a**. An identical analysis of **99e**[87] results in the same conclusion, and was verified by the isolation and identification, using 2D-NOESY NMR spectroscopy, of **100**.

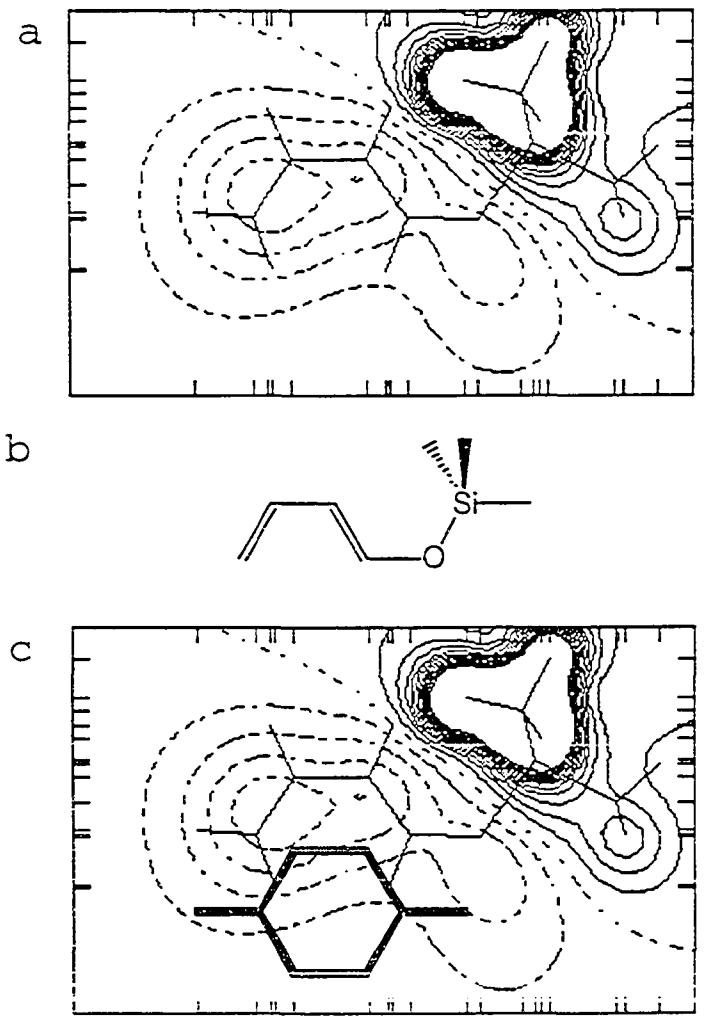


Figure 2. (a) RHF/6-31G(d)//AM1 MEP of 1-trimethylsilyloxy-1,3-butadiene evaluated in a plane 2 Å above the plane of symmetry. The contour spacing is 5 kcal/mol·e. (b) Schematic orientation of the molecule in the MEP. (c) Same as (a) but with part of the dienophile structure superimposed (bold lines) to show the regions of the MEP likely to interact with the dienophile substituents as the diene approaches

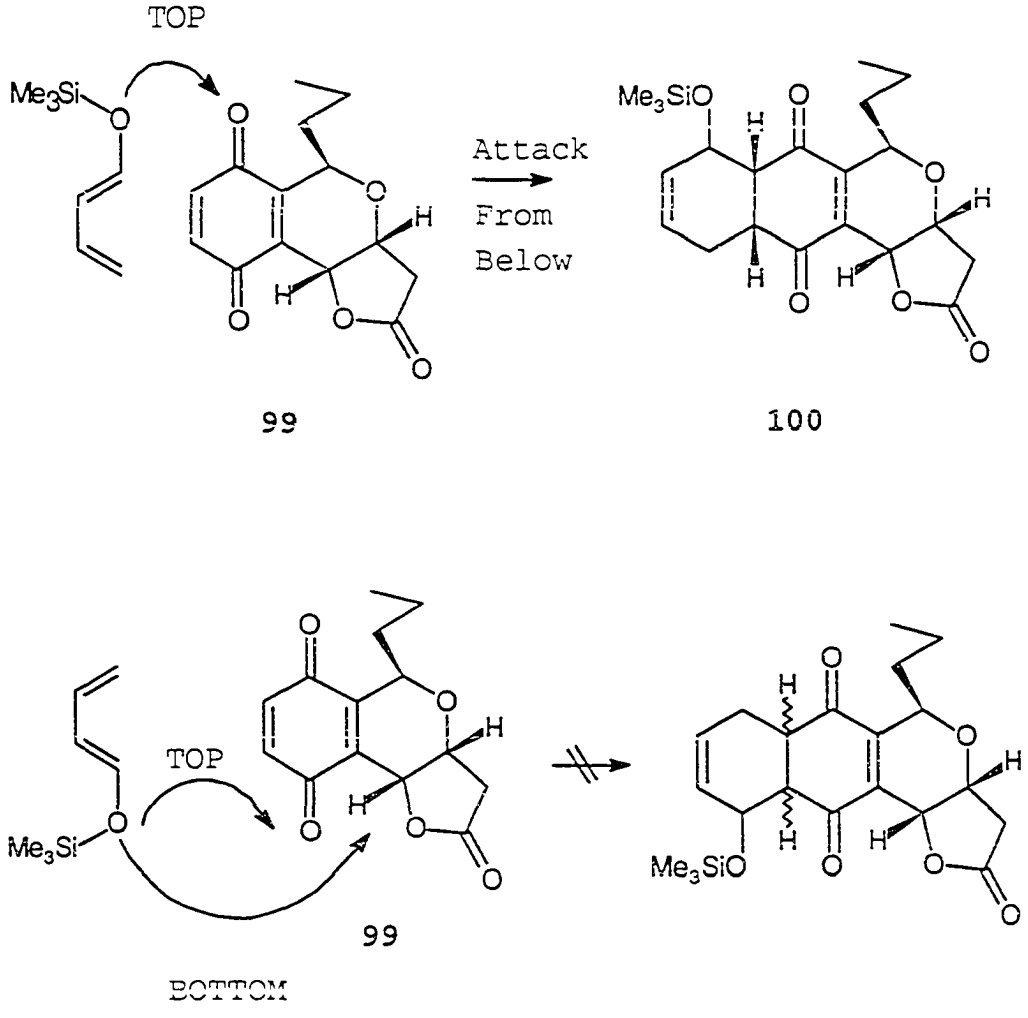


Figure 3 Schematic depiction of the four possible approaches of the dienophile when reacting with **99a**. The curved arrows represent electrostatic repulsions suggested by the MEPs in Figures 1 and 2 that disfavor that approach.

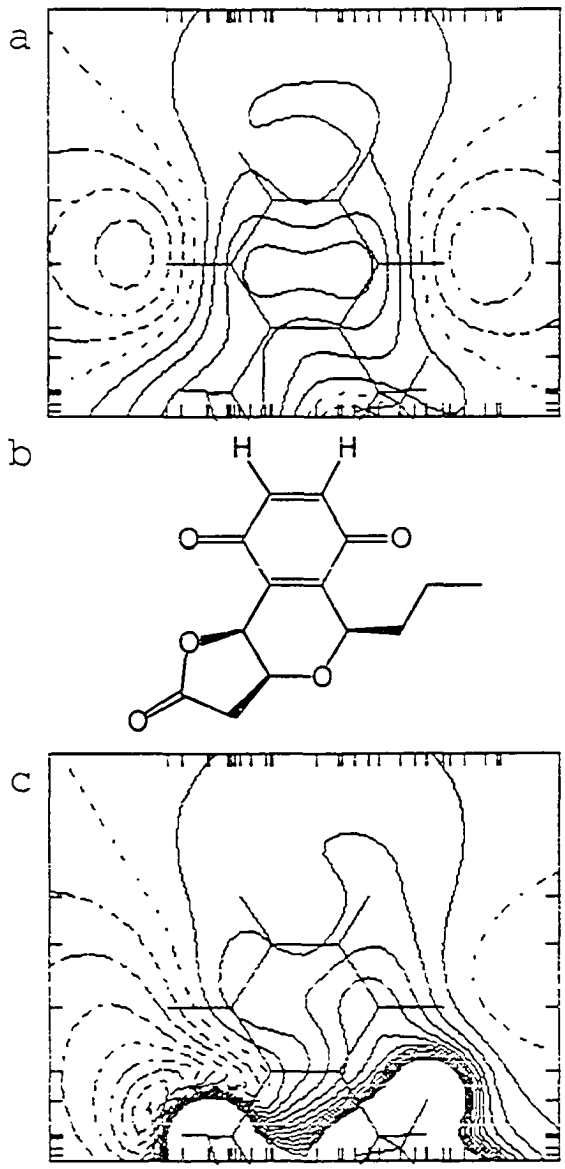


Figure 4 MEPs of **106a** evaluated in planes 2 Å below (a) and above (c) the DP plane. The contour spacing is 5 kcal/mol•e. (b) Schematic orientation of **106a** in the MEPs

Figure 4 shows MEPs for **106a** that are analogous to those in Figure 1. These MEPs indicate that the diene should prefer to react with **106** from *above* the plane of the ring, and with the OTMS substituent away from the butyrolactone ring.

The observed regioselectivity thus appears to be dictated by the unequal charge distribution and the molecular geometry. The quinone oxygens force the reaction to occur on one face of the quinone ring, where the butyrolactone ring oxygen directs the OTMS substituent away from the butyrolactone ring. The fact that the quinone oxygens disfavor one ring face indicates that the the quinone ring is non-planar. Figure 5a shows that the quinone ring of **99a** is indeed puckered such that the two quinone oxygens are bent above the DP plane, disfavoring attack from above (Figure 1c). The degree of puckering can be gauged by the dihedral angles between the oxygens and the alkene carbons, defined as τ and τ' in Figure 5; both would be 180° for a planar ring. For **99a**, τ and τ' equal 164° and -170°, a 10°-15° deviation from planarity (negative and positive dihedral angles refer to clockwise and counter-clockwise rotation around the center bond; cf. Figure 5b). Figure 5c shows a similar puckering of the quinone ring of **106a**, but in the opposite direction – away from the butyrolactone ring. The deviation from planarity for **106a** is only slighty less than

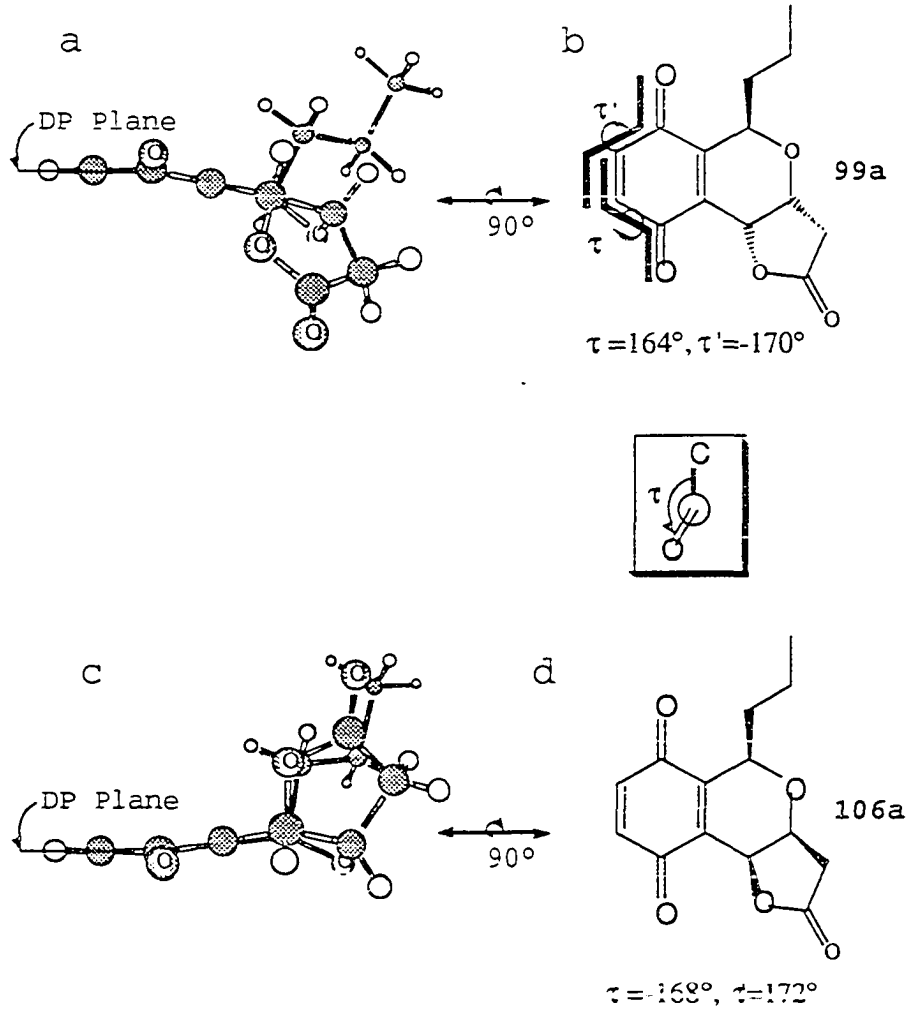
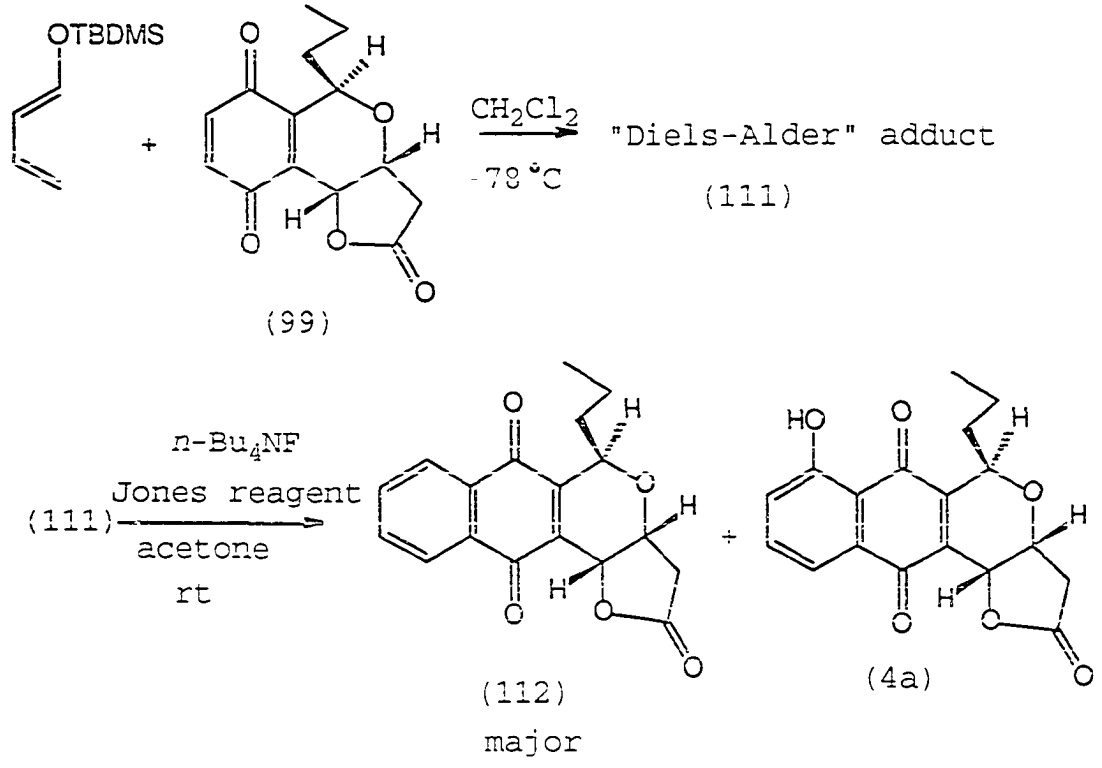


Figure 5 (a) Side view of the AM1 optimized structure of **99a** showing the puckering of the quinone ring. (b) Schematic view of **99a** and definition of the two dihedral angles used to quantify the deviation from planarity for the quinone oxygens. (c) Side view of the AM1 optimized structure of **106a** showing the puckering of the quinone ring. (d) Schematic view of **106a**

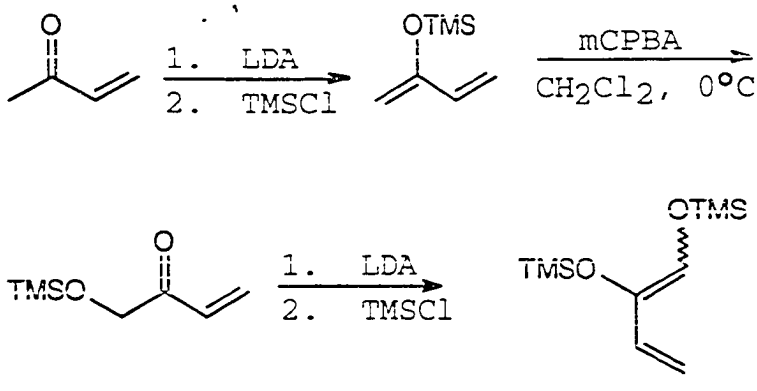
for **99a**, with τ and τ' values of -168° and 172°, respectively. Therefore, it appears that the butyrolactone ring induces the quinone ring-puckering that contributes to the regioselectivity.

To further understand the origins of the selectivity of the Diels-Alder reaction, we have tested several different dienes. A more stable 1-(*tert*-butyldimethylsilyloxy)-1,3-*trans*-butadiene was prepared from *tert*-butyldimethylsilyl chloride, crotonaldehyde, and triethylamine according to the method of House.[88] Treatment of this diene with quinone **99** in methylene chloride afforded Diels-Alder reaction adduct **111.** The adduct **111** was then treated with Jones reagent



under the same conditions used for the preparation of frenolicin B; unfortunately, only starting material was recovered. A mixture of Jones reagent and tetra-*n*-butylammonium fluoride could convert the adducts to 7-dehydroxyfrenolicin B (**112**); only minor frenolicin B (**4a**) was obtained from this reaction. It was assumed that removal of the TBDMS group was more difficult than elimination of the TBDMSO group in this molecule. Therefore, various methods including *n*-Bu_4NF, 45% HF, HF-Et_3N, Ph_3CBF_4, and acetic acid were tested to cleave the Si-O bond; unfortunately, all these efforts induced only 7-dehydroxyfrenolicin B (**112**).

An effort to make Arizonins,[8,9] a new group of antibiotics, was also attempted. 1,2-bistrimethylsilyloxy-1,3-butadiene (**113**) was prepared by several steps. Unfortunately, treatment of quinone **104** with diene **113** did not give any of the desired product.



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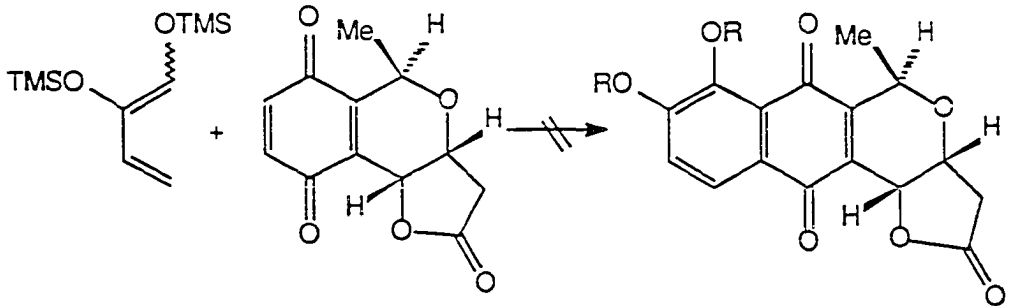
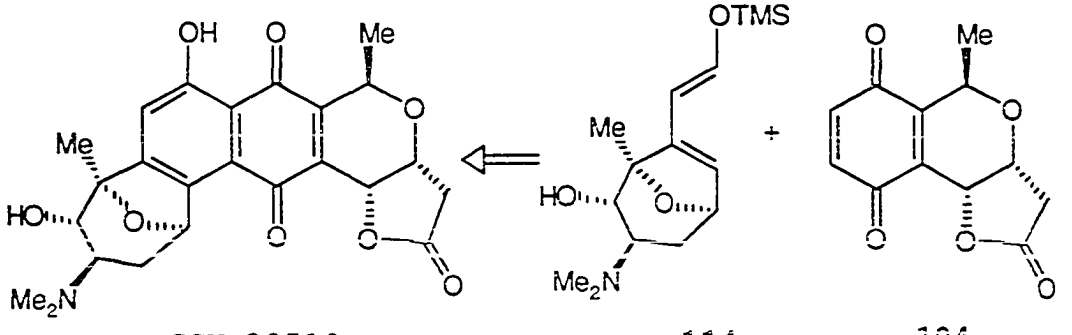
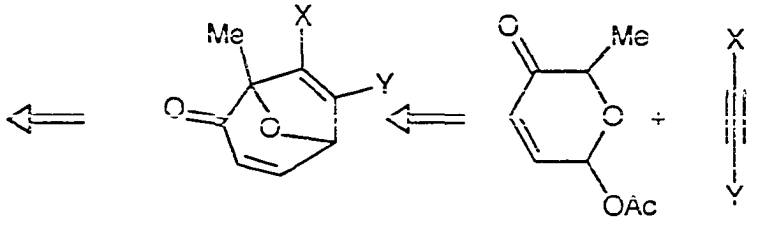


113 **104**

Our next target was SCH 38519, a more complex pyranonaphthoquinone compound.[14] Retrosynthesis of SCH 38519 was outlined below. Efforts to make the diene **114** is in progress.



SCH-38519 **114** **104**



CONCLUSION

Frenolicin B (**4a**), α,β-epoxyfrenolicin B (**5a, 5b**), 5-epi-frenolicin (**4b**), and 7-deoxyfrenolicin (**112**) have been synthesized in six to seven steps from asymmetric alcohol **92**. Racemic kalafungin (**6**), an antifungal agent, has been synthesized in five steps from diol **102**. The key step in all syntheses, a regioselective Diels-Alder reaction, proceeds with complete regiocontrol and in excellent yield. One rationale for the remarkable stereocontrol is that the lactone ring induces ring-puckering in the quinone subunit which, in consort with electrostatic repulsion, contributes to the regioselectivity.

EXPERIMENTAL

Unless otherwise noted, materials were obtained from commercial suppliers and were used without purification. Diethyl ether and tetrahydrofuran (THF) were distilled from sodium benzophenone ketyl. Benzene was distilled from lithium aluminum hydride. Methylene chloride and acetonitrile were purified by distillation from calcium hydride. Apparatus for experiments requiring anhydrous conditions were flame-dried under a stream of argon or dried in a 150 °C oven for 12 h and cooled under a stream of argon or in a desiccator. Flash chromatography was performed on EM Science Kieselgel 60 (mesh 230-400). Thin layer chromatography was performed using Merck TLC plates (silica gel 60) with a thickness of 0.25 mm. The solvent system was suitable mixtures of hexane (H) and ethyl acetate (EA) unless otherwise noted. The abbreviation sg represents silica gel. Infrared spectra were obtained on a Bio-Rad FTS-7 spectrophotometer and are reported in cm^{-1}. Proton nuclear magnetic resonance spectra (300 MHz) were obtained using a Nicolet Magnetic Corporation NT-300 spectrometer. All chemical shifts are reported in δ relative to tetramethylsilane as an internal standard. Splitting patterns are designated as s (singlet), d (doublet), t (triplet), q (quartet), dd (doublet of doublets), dt (doublet of

triplets), ABq (AB quartet), and m (multiplet); a br prefix indicates a broadened pattern. Carbon-13 NMR spectra were obtained on a Nicolet Magnetic Corporation NT-300 spectrometer and are reported in δ relative to $CDCl_3$ (77.00 ppm. High resolution mass spectra were obtained on a Kratos model MS-50 spectrometer. Low resolution mass spectra were obtained on a Finnegan 4023 mass spectrometer. Melting points were determined on a Fisher-Johns melting point apparatus and are uncorrected. Optical rotations were obtained using a JASCO DIP-370 digital polarimeter. The purity of all title compounds was determined to be >95% by 300 MHz proton NMR and/or elemental analysis.

R-2,5-Dimethoxyphenyl propyl carbinol (92). (Method 1). A solution of (+)-Ipc_2BCl (10 g, 31 mmol) in THF (20 mL) was cooled to -25 °C and 2,5-dimethoxybutyrophenone (5.4 g, 26 mmol) was added. The reaction solution was stirred at -25 °C and monitored by TLC. When the reaction was complete, the mixture was raised to room temperature (rt) and THF was removed at aspirator pressure. The α-pinene liberated during the reaction was removed *in vacuo*. The residue was dissolved in 100 mL of ethyl ether, diethanolamine (6.28 g, 60 mmol) was added, and the mixture stirred for 3 h. The resulting solid was filtered off and washed with pentane (2 x 50 mL). The combined filtrates were concentrated. The residue was

purified by sgc using 6:1 H:EA. The yield of alcohol **92** was 99% (5.4 g): $[\alpha]_D^{25°C}$=24.6° (C 2.2, CH_2Cl_2).

(Method 2). To a vigorously stirred solution of 2,5-dimethyoxybenzaldehyde (10.0 g, 60.2 mmol) and quinine (1.4 g, 4.32 mmol) in dry ether (300 mL) at 0 °C was added dropwise (via syringe) dipropylzinc (15.3 g, 101.2 mmol). The solution was allowed to warm to rt and stirred for 48 h. The reaction was quenched at 0 °C by the addition of 2 N HCl. The aqueous layer was extracted three times with ether. The organic layers were dried and concentrated. The alcohol was purified by sg chromatography using 8:1 hexane:ethyl acetate. The yield of alcohol was 83%: $[\alpha]_D^{25°C}$=18.1° (C 3.5, CH_2Cl_2); ^1H NMR ($CDCl_3$) δ 0.94 (t, *J* = 7.5 Hz, 3 H), 1.24-1.85 (m, 4 H), 3.78 (s, 3 H), 3.81 (s, 3 H), 4.84 (dd, *J* = 5.7, 7.5 Hz, 1 H), 6.72-6.83 (m, 2 H), 6.89 (d, *J* = 3.0 Hz, 1 H); IR (neat) 3438, 1496, 1464, 1275, 1214, 1177, 1027 cm^{-1}; TLC (H:EA = 4:1) R_f=0.5.

R- 2,5-Dimethoxy-6-(1-hydroxy-2-propenyl)phenyl propyl carbinol (94a). To the benzylic alcohol **92**(4.3 g, 20.4 mmol) in 220 mL of 1:10 ether:pentane at 0°C was added *n*-BuLi (19.8 mL, 43 mmol) dropwise with vigorous stirring. The solution was allowed to warm to rt and stirred for 24 h. The solution was then cooled to -78 °C and a solution of acrolein (3.0 mL, 45 mmol) in 10 mL of pentane was added. After the reaction

had stirred for 8 h at -78 °C, it was quenched with saturated ammonium chloride solution and extracted 5 times with ether/ethyl acetate. The organic layers were dried and concentrated. Purification by sgc using 8:1, then 4:1 hexane:ethyl acetate, followed by recrystallization from CH_2Cl_2/hexane, afforded 42% of the desired diastereomer, and 25% of the undesired diastereomer. ^1H NMR ($CDCl_3$) δ 0.94 (t, J = 7.2 Hz, 3 H), 1.33-1.65 (m, 4 H), 1.88-2.20 (m, 1 H), 3.81 (s, 3 H), 3.83 (s, 3 H), 5.06-5.22 (m, 2 H), 5.65-5.75 (m, 1 H), 6.13-6.26 (m, 1 H), 6.76-6.82 (m, 2 H); IR ($CDCl_3$) 3606, 3541, 3153, 2960, 2837, 1475, 1464, 1250, 1228, 921, 755cm^{-1}; MS: m/e 91, 103, 121, 146, 162, 177, 205, 223, 248, 266; HRMS: for $C_{15}H_{22}O_4$ calcd. 266.1518, measured 266.1513; CMR ($CDCl_3$) δ 14.0, 19.6, 39.5, 55.7, 55.9, 69.6, 70.0, 110.3, 110.5, 114.3, 129.1, 131.9, 140.2, 151.9; TLC (H:EA = 2:1) R_f=0.34.

General Procedure for the Palladium-mediated Cyclization Reaction

A mixture of diol (2.6 mmol), palladium acetate (0.78 mmol) and $CuCl_2$ (0.85 g, 6.3 mmol) in 50 mL of THF under an atmosphere of CO was vigorously stirred for 24 h. The mixture was concentrated and purified by sgc using hexanes:ethyl acetate.

R,R,R-6,9-Dimethoxy-3, 3a, 5, 9b-tetrahydro-5-propylfuro[3,2-c][2]benzopyran-2-one (95). Purified by sgc using 6:1, then 4:1 H:EA and recrystallization from methylene chloride/hexane gave **95**. The yield was 61%. ^{1}H NMR ($CDCl_3$) δ 0.99 (t, J = 7.2 Hz, 3 H), 1.45-1.78 (m, 4 H), 2.66 (d, J = 17.7 Hz, 1 H), 2.91 (dd, J = 4.8, 17.4 Hz, 1 H), 3.79 (s, 3 H), 3.84 (s, 3 H), 4.61 (dd, J = 3.0, 5.1 Hz, 1 H), 4.96 (dd, J = 3.9, 9.9 Hz, 1 H), 5.33 (d, J = 2.7 Hz, 1 H), 6.80 (ABq, 2 H); IR ($CDCl_3$) 3004, 2958, 2937, 2872, 2837, 1777, 1604, 1486, 1463, 1430, 1263, 1201, 1156, 1077 cm^{-1}; MS: m/e 55, 77, 91, 121, 145, 162, 177, 190, 203, 221, 249, 292; HRMS: for $C_{16}H_{20}O_5$ calcd. 292.1311, measured 292.1311; CMR ($CDCl_3$) δ 13.7, 19.4, 33.6, 37.5, 55.7, 56.1, 65.7, 70.7, 71.6, 108.9, 111.5, 117.1, 129.6, 148.6, 152.5, 175.4; TLC (H:EA = 2:1) R_f=0.40; $[\alpha]_D^{25°C}$=174.0° (C 0.80, CH_2Cl_2).

R*,R*,R*-6,9-Dimethoxy-3, 3a, 5, 9b-tetrahydro-5-methylfuro [3,2-c][2]benzopyran-2-one (103). Purified by sgc using 4:1 H:EA. The yield was 51%. ^{1}H NMR ($CDCl_3$) δ 1.47 (d, J = 6.6 Hz, 3 H), 2.63-2.96 (m, 2 H), 3.79 (s, 3 H), 3.84 (s, 3 H), 4.69 (dd, J = 2.7, 4.8 Hz, 1 H), 5.15 (q, J = 6.6 Hz, 1 H), 5.34 (d, J = 2.4 Hz, 1 H), 6.75-6.86 (ABq, 2 H); IR ($CDCl_3$) 3154, 2938, 2837, 1781, 1603, 1486, 1438, 1404, 1321, 1296, 1262, 1205, 1157, 1078, 988, 921, 755 cm^{-1}; MS: m/e 55, 77, 91, 103, 121, 145, 162, 190, 203, 221, 233, 249, 264; HRMS:

m/e for $C_{14}H_{16}O_5$ calcd. 264.0998, measured 264.0996; CMR ($CDCl_3$) δ 18.1, 37.3, 55.3, 55.7, 65.7, 67.0, 71.3, 108.7, 111.2, 116.5, 129.6, 148.2, 152.1, 175.4; TLC (H:EA = 2:1) R_f=0.29.

R,S,S-6,9-Dimethoxy-3, 3a, 5, 9b-tetrahydro-5-propylfuro[3,2-c][2]benzopyran-2-one (105). To a solution of the diol **94b** (0.80 g, 3.0 mmol) in THF-H_2O (3:1, 40 mL) was added mercuric acetate (1.05 g, 3.3 mmol) and the solution was stirred at rt overnight. The solution was diluted with saturated NaCl solution and extracted three times with ether. The organic layers were dried with magnesium sulfate and concentrated *in vacuo*. The resulting mercurial could be used directly in the next step.

Anhydrous lithium chloride (0.085 g, 2.0 mmol), palladium chloride (0.177 g, 1.0 mmol), barium oxide (0.153 g, 1.0 mmol) and 5 mL of THF were placed in a dried 25 mL round bottom flask. The flask was flushed thoroughly with carbon monoxide and 0.5 g (1.0 mmol) of the mercurial was added. A balloon filled with carbon monoxide was connected to the flask, and the reaction mixture was stirred 24 h at rt. The mixture was filtered, and the filtrate was dried over magnesium sulfate and concentrated *in vacuo*. The residue was purified by sgc using 4:1 H:EA to afford 0.091 g (31% over two steps) of **105**. ^1H NMR ($CDCl_3$) δ 0.84 (t, J =

7.5 Hz, 3 H), 1.05-1.4 (m, 2 H), 1.82-2.05 (m, 2 H), 2.67-2.87 (m, 2 H), 3.78 (s, 3 H), 3.84 (s, 3 H), 4.27 (dd, J = 2.1, 3.9 Hz, 1 H), 4.84 (dd, J = 3.0, 5.4 Hz, 1 H), 5.33 (d, J = 1.5 Hz, 1 H), 6.82 (ABq, 2 H); IR ($CDCl_3$) 3003, 2958, 2934, 2838, 1783, 1602, 1484, 1438, 1349, 1292, 1259, 1204, 1153, 1086, 1041, 980, 802, 736 cm^{-1}; MS: m/e 84, 115, 149, 165, 207, 222, 249, 292; HRMS: m/e for $C_{16}H_{20}O_5$ calcd. 292.1311, measured 292.1309; CMR ($CDCl_3$) δ 14.1, 17.7, 36.1, 38.2, 55.5, 55.9, 70.6, 72.5, 72.6, 108.9, 112.0, 118.1, 129.0, 149.5, 152.6, 175.9; TLC (H:EA = 2:1) R_f=0.40.

General Procedure for the Oxidation of Hydroquinone Dimethyl Ethers

To a suspension of silver oxide (AgO, Aldrich Chemical Co., 0.18g, 1.15 mmol) and tricyclic lactone (0.36 mmol) in 9 mL of THF at rt was added 6N HNO_3 (0.36 mL, 2.17 mmol). After the starting material was gone by TLC, the reaction was worked up by the addition of 20 mL of ether and 5 mL of water. The aqueous layer was extracted three times with ether. The combined organic layers were washed with brine, dried over sodium sulfate and concentrated *in vacuo*. The residue was purified by sgc.

R,R,R-3, 3a, 5, 9b-Tetrahydro-5-propylfuro[3,2-c][2] benzopyran-2,6,9-trione (99). Purification using 2:1 H:EA

afforded a 100% yield of tricyclic quinone. ^{1}H NMR ($CDCl_3$) δ 0.99 (t, J = 7.2 Hz, 3 H), 1.50-1.75 (m, 4 H), 2.68 (d, J = 17.7 Hz, 1 H), 2.93 (dd, J = 5.4, 17.7 Hz, 1 H), 4.57 (dd, J = 3.3, 5.1 Hz, 1 H), 4.73 (dd, J = 4.5, 8.7 Hz, 1 H), 5.09 (d, J = 3.0 Hz, 1 H), 6.84 (ABq, 2 H); IR ($CDCl_3$) 2962, 2933, 2873, 1793, 1665, 1299, 1197, 1149, 1002 cm^{-1}; MS: m/e 56, 77, 91, 99, 115, 135, 147, 161, 175, 191, 219, 262; HRMS: for $C_{14}H_{14}O_5$ calcd. 262.0841, measured 262.0840; CMR ($CDCl_3$) d 13.4, 19.3, 33.4, 36.7, 66.1, 68.4, 69.5, 132.1, 136.4, 136.5, 146.8, 174.0, 184.3, 185.1; TLC (H:EA = 2:1) R_f=0.32; $[\alpha]_D^{25°C}$=59.9° (C 1.28, CH_2Cl_2).

R*,R*,R*-3, 3a, 5, 9b-tetrahydro-5 methylfuro[3,2c][2] benzopyran-2,6,9-trione (104). Purification using 2:1 H:EA afforded a 91% yield of tricyclic quinone. ^{1}H NMR ($CDCl_3$) δ 1.48 (d, J = 6.9 Hz, 3 H), 2.64-2.98 (m, 2 H), 4.84 (dd, J = 3.0 Hz, 5.1 Hz, 1 H), 4.91 (q, J = 6.9 Hz, 1 H), 5.09 (d, J = 3.0 Hz, 1 H), 6.85 (ABq 2 H); IR ($CDCl_3$) 2983, 2938, 2874, 1792, 1667, 1308, 1198, 1149, 922, 896, 841, 756, 652 cm^{-1}; MS: m/e 151, 163, 175, 179, 191, 219, 234; HRMS: m/e for $C_{12}H_{10}O_5$ calcd. 234.0528, measured 234.0531; CMR ($CDCl_3$) δ 18.5, 36.8, 66.2, 66.4, 68.3, 132.1, 136.5, 147.3, 174.0, 184.3, 185.1; TLC (H:EA = 2:1) R_f=0.27.

R,S,S-3, 3a, 5, 9b-tetrahydro-5-propylfuro[3,2-c][2] benzopyran-2,6,9-trione (106). (Method 1, general procedure). Oxidation of **105** and purification using 2:1 H:EA afforded a 95% yield of tricyclic quinone **106.**

(Method 2). To a solution of **109** in 100 mL of acetonitrile at room temperature was added ceric ammonium nitrate (7.95 g, 14.5 mmol) in 20 mL of water. After 10 minutes, the reaction was quenched with 20 mL of pH 7.0 buffer and extracted with methylene chloride. The organic phase was washed with water, brine, dried over magnesium sulfate, filtered, and concentrated *in vacuo*. Flash chromatography (H:EA/3:1) gave **110** (0.73 g, 45% yield).

To a solution of trione **110** (0.255 g, 0.92 mmol) in 10 mL of dry methylene chloride at -78 °C was added triethylsilane (0.35 mL, 2.20 mmol) followed by the dropwise addition of boron trifluoride etherate (0.17 mL, 1.38 mmol). The reaction was stirred at -78 °C for 12 h and then quenched with 5 mL of water. The aqueous layer was extracted with methylene chloride, and the combined organic layers were washed with brine, dried over magnesium sulfate, filtered, and concentrated *in vacuo*. Flash chromatography (H:EA/4:1) gave **106** (0.102 g, 42% yield). ^{1}H NMR ($CDCl_3$) δ 0.89 (t, J = 7.5 Hz, 3 H), 1.20-1.46 (m, 2 H), 1.78-2.02 (m, 2 H), 2.69-2.91 (m, 2 H), 4.30 (dd, J = 2.7, 4.5 Hz, 1 H), 4.60-4.63 (m, 1 H), 5.11 (t, J = 2.1 Hz, 1 H), 6.84 (ABq, 2 H); IR ($CDCl_3$)

2963, 2932, 2874, 1791, 1663, 1602, 1405, 1324, 1299, 1260, 1203, 1149, 1048, 1004, 909, 842 cm^{-1}; MS: m/e 97, 127, 175, 191, 220, 262; HRMS: m/e for $C_{14}H_{14}O_5$ calcd. 262.0841, measured 262.0846; CMR ($CDCl_3$) δ 14.2, 18.3, 35.3, 37.2, 69.3, 70.9, 71.5, 133.3, 136.1, 137.1, 147.5, 174.5, 184.0, 185.8, ; TLC (H:EA = 2:1) R_f=0.35.

Furo[2,3-b]benzofuran-4-(1-oxobutyl)-3a,8b-dihydro-5-hydroxy-1-one (109). To a solution of keto phenol **107** (1.50 g, 8.33 mmol) in 50 mL of dry ethyl ether was added magnesium sulfate (2.51 g, 20.8 mmol) and freshly prepared silver(I) oxide (4.83 g, 20.8 mmol) at room temperature. After stirring 5 h, the inorganic solids were removed and the solution was evaporated to give 1.11 g of trione **108**. The yield was 75%. Proton NMR spectroscopy showed that crude product **108** was pure enough to undergo the next step.

To the solution of trione **108** (1.11 g, 6.24 mmol) in 40 mL of dry methylene chloride at -78 °C was added 2-(trimethylsilyoxy)furan (1.26 mL, 7.48 mmol). The reaction was stirred at -78 °C for 4 h and then slowly warmed up to room temperature over 12 h. The solvent was evaporated and the residue purified by sg chromatography using 3:1/H:EA to afford **109** (1.52 g, 93% yield). ^1H NMR ($CDCl_3$) δ 1.04 (t, J = 7.5 Hz, 3 H), 1.74-1.87 (m, 2 H), 2.89-3.00 (m, 2 H), 3.01-3.16 (m, 2 H), 3.21-3.32 (m, 1 H), 5.39 (dt, J = 2.4, 3.3 Hz,

1 H), 6.32 (d, J = 6.0 Hz, 2 H), 7.02-7.09 (m, 2 H), 12.62 (s, 1H); IR ($CDCl_3$) 2967, 2877, 1786, 1640, 1478, 1441, 1240, 1189, 1149, 1070, 1044, 988, 830 cm^{-1}; MS: m/e 121, 146, 171, 203, 220, 247. 262; HRMS: m/e for $C_{14}H_{14}O_5$ calcd. 262.0841, measured 262.0842; CMR ($CDCl_3$) δ 13.6, 16.9, 35.3, 43.5, 80.6, 84.4, 116.2, 119.1, 119.7, 123.3, 153.8, 158.5, 173.9, 205.3; TLC (H:EA = 2:1) R_f=0.52.

General Procedure for the Diels-Alder/oxidation

To a solution of the tricyclic quinone (0.12 mmol) in 1 mL of methylene chloride at -78 °C was added dropwise 1-(trimethylsilyloxy)-1,3-butadiene (0.025 mL, 0.14 mmol). The solution was stirred at -78 °C for 4.5 hours (starting material remained by TLC) and then allowed to slowly warm to rt overnight. The solvent was removed *in vacuo*.

The residue was dissolved in 1.5 mL of acetone and 2.7 M Jones reagent (0.09 mL, 0.24 mmol) was added at 0 °C. The reaction was stirred for 40 min. The solution was concentrated *in vacuo*. The residue was partitioned between saturated ammonium chloride solution (10 mL) and ether (100 mL). The organic layer was washed with saturated NH_4Cl solution and brine and then dried over sodium sulfate. The solvent was concentrated *in vacuo* and the residue was purified by sgc.

Frenolicin B (4a). Purified using 4:1 H:EA. The yield over two steps was 81%. ^{1}H NMR ($CDCl_3$) δ 1.03 (t, *J* = 7.2 Hz, 3 H), 1.5-1.85 (m, 4 H), 2.71 (d, *J* = 17.7 Hz, 1 H), 2.96 (dd, *J* = 5.1, 17.7 Hz, 1 H), 4.62 (dd, *J* = 3.3, 5.1 Hz, 1 H), 4.91 (dd, *J* = 3.0, 9.9 Hz, 1 H), 5.26 (d, *J* = 3.0 Hz, 1 H), 7.25-7.35 (m, 1 H), 7.62-7.76 (m, 2 H), 11.84 (s, 1 H); IR ($CDCl_3$) 2962, 2933, 2874, 1791, 1652, 1624, 1457, 1283, 1245, 1194, 1148cm^{-1}; MS: m/e 55, 92, 121, 139, 157, 173, 201, 213, 225, 229, 241, 257, 285, 300, 328; HRMS: for $C_{18}H_{16}O_6$ calcd. 328.0947, measured 328.0941; CMR ($CDCl_3$) δ 13.5, 19.5, 33.7, 36.8, 66.2, 68.7, 69.6, 114.8, 119.7, 124.8, 131.4, 135.1, 137.1, 149.2, 161.8, 173.8, 181.4, 187.9; TLC (H:EA = 2:1) R_f=0.45; $[\alpha]_D^{25°C}$=226.0° (C 0.84, CH_2Cl_2).

Kalafungin (6). Purified using 4:1 H:EA. The yield over two steps was 51%. ^{1}H NMR ($CDCl_3$) δ 1.57 (d, *J* = 6.9 Hz, 3 H), 2.67-3.01 (m, 2 H), 4.69 (dd, *J* = 3.0, 4.8 Hz, 1 H), 5.09 (q, *J* = 6.9 Hz, 1 H), 5.26 (d, *J* = 3.0 Hz, 1 H), 7.30 (dd, *J*=1.8, 7.5 Hz, 1 H), 7.64-7.72 (m, 2 H), 11.84 (s, 1 H); IR ($CDCl_3$) 2937, 1791, 1667, 1651, 1623, 1575, 1457, 1368, 1284, 1243, 1194, 1150, 922, 897, 716, 652 cm^{-1}; MS: m/e 70, 121, 201, 229, 241, 257, 300; HRMS: m/e for $C_{16}H_{12}O_6$ calcd. 300.0634, measured 300.0625; CMR ($CDCl_3$) δ 18.4, 38.8, 66.2, 66.5, 68.7, 114.6, 119.5, 124.8, 131.2, 135.1, 139.0, 149.9, 161.7, 174.3, 181.5, 187.8; TLC (H:EA = 1:1) R_f=0.46.

5-Epi-frenolicin B (4b). Purified using 4:1 H:EA. The yield over two steps was 63%. ^{1}H NMR ($CDCl_3$) δ 0.90 (t, J = 7.3 Hz, 3 H), 1.25-1.55 (m, 2 H), 1.86-2.12 (m, 2 H), 2.70-2.95 (m, 2 H), 4.34 (dd, J = 1.8, 2.4 Hz, 1 H), 4.33-4.78 (m, 1 H), 5.28 (t, J = 1.8 Hz, 1 H), 7.26-7.32 (m, 1 H), 7.62-7.70 (m, 1 H), 11.73 (s, 1 H); IR ($CDCl_3$) 2962, 2931, 1792, 1668, 1645, 1618, 1457, 1284, 1247, 1148, 1048, 730 cm^{-1}; MS: m/e 92, 121, 173, 201, 227, 241, 257, 286, 328; HRMS: m/e for $C_{18}H_{16}O_6$ calcd. 328.0947, measured 328.0953; CMR ($CDCl_3$) δ 13.9, 18.2, 35.9, 69.7, 70.8, 71.8, 114.9, 119.5, 124.8, 131.3, 136.1, 137.0, 149.6, 161.6, 174.3, 181.3, 188.6; TLC (H:EA = 2:1) R_f=0.47.

7-Dehydroxyfrenolicin B (112). To solution of the tricyclic quinone **99** (0.10 g, 0.38 mmol) in 3 mL of dry methylene chloride at -78 °C was added dropwise 1-(t-butyldimethylsilyloxy)-1,3-butadiene (0.28 g, 0.15 mmol). The solution was stirred at -78 °C for 8 hours and then allowed to slowly warm to rt overnight. The reaction was stirred at room temperature for another 48 h until the starting material had disappeared. The resulting Diels-Alder adduct could be used directly in the next step.

To the above reaction solution was added triphenylcarbenium tetrafluoroborate (0.85 g, 2.58 mmol) at room temperature. The reaction was stirred at room

temperature and quenched with 5 mL of water. The aqueous phase was extracted twice by methylene chloride. The organic layer was washed with saturated NaCl solution and then dried over magnesium sulfate. The solvent was concentrated *in vacuo* and the residue was purified by sgc (H:EA/4:1) to afford **112** (0.056 g, 47%). ^{1}H NMR ($CDCl_3$) δ 1.02 (t, *J* = 6.9 Hz, 3 H), 1.52-1.85 (m, 4 H), 2.68-3.00 (m, 2 H), 4.63 (dd, *J* = 3.3, 5.1 Hz, 1 H), 4.91 (dd, *J* = 2.7, 9.9 Hz, 1 H), 5.29 (d, *J* = 3.0 Hz, 1 H), 7.76-7.82 (m, 1 H), 8.08-8.19 (m, 2 H); IR ($CDCl_3$) 2963, 2933, 2874, 1793, 1670, 1624, 1290, 1197, 1150 cm^{-1}; MS: m/e 100, 141, 162, 181, 225, 241, 269, 284, 312; HRMS: for $C_{18}H_{16}O_5$ calcd. 312.0998, measured 312.0989; CMR ($CDCl_3$) δ 19.5, 29.7, 33.6, 36.9, 66.2, 68.2, 68.9, 69.9, 126.5, 126.6, 131.5, 131.6, 134.2, 134.4, 148.9, 174.1, 182.2, 183.0; TLC (H:EA = 2:1) R_f=0.45.

The Procedure for Preparation of α, β-Epoxyfrenolicin B

To a solution of frenolicin B (0.06 g, 0.183 mmol) and *t*-BuOOH (0.64 mmol) in dry benzene was added Triton B in 40% methanol. The solution was then warmed up to 55 °C and stirred overnight. The solvent was evaporated and residue was purified by sg chromatography using H:EA/5:1 to afford α-epoxyfrenolicin B (0.051 g, 73% yield) and β-epoxyfrenolicin B (0.0105 g, 15% yield).

α-Epoxyfrenolicin B (101a). ^{1}H NMR ($CDCl_3$) δ 1.02 (t, *J* = 7.5 Hz, 3 H), 1.48-2.0 (m, 4 H), 2.58-2.93 (m, 2 H), 4.49 (dd, *J* = 5.4, 6.0 Hz, 1 H), 4.91 (dd, *J* = 2.7, 11.4 Hz, 1 H), 5.46 (d, *J* = 4.5 Hz, 1 H), 7.28-7.32 (m, 1 H), 7.56-7.71 (m, 2 H), 11.32 (s, 1H); IR ($CDCl_3$) 3537, 2961, 2934, 2874, 1789, 1700, 1652, 1575, 1454, 1162, 927; MS: m/e 121, 189, 216, 245, 273, 302, 344 cm^{-1}; HRMS: for $C_{18}H_{16}O_7$ calcd. 344.0896, measured 344.0890; CMR ($CDCl_3$) δ 13.4, 18.5, 28.6, 35.2, 59.9, 64.1, 64.4, 67.3, 69.5, 114.0, 119.7, 124.9, 131.1, 137.4, 161.9, 174.3, 188.1, 193.8; TLC (H:EA = 2:1) R_f=0.40; $[\alpha]_D^{25°C}$=6.6° (C 1.12, CH_2Cl_2).

β-Epoxyfrenolicin B (101b). ^{1}H NMR ($CDCl_3$) δ 1.03 (t, *J* = 6.9 Hz, 3 H), 1.46-1.80 (m, 4 H), 2.54-2.79 (m, 2 H), 4.38 (d, *J* = 0.9 Hz, 1 H), 4.91 (dd, *J* = 3.0, 10.5 Hz, 1 H), 5.03 (d, *J* = 1.8 Hz, 1 H), 7.32-7.34 (m, 1 H), 7.66-7.73 (m, 2 H), 11.44 (s, 1H); IR ($CDCl_3$) 2961, 2934, 2874, 1797, 1702, 1651, 1575, 1454, 1143, 1060, 940; MS: m/e 121, 189, 216, 245, 273, 301, 344 cm^{-1}; HRMS: for $C_{18}H_{16}O_7$ calcd. 344.0896, measured 344.0887; CMR ($CDCl_3$) δ 13.9, 18.7, 30.4, 38.6, 60.7, 65.0, 66.1, 67.7, 71.9, 113.4, 119.9, 125.1, 130.8, 137.4, 162.2, 174.0, 185.5, 194.0; TLC (H:EA = 2:1) R_f=0.65; $[\alpha]_D^{25°C}$=149.8° (C 0.42, CH_2Cl_2).

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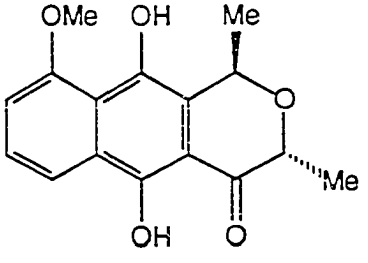
PAPER II

REGIOCONTROL BY REMOTE SUBSTITUENTS. DIRECT TOTAL SYNTHESIS OF HONGCONIN

INTRODUCTION

Hongconin (**1**) is a novel naphthohydroquinone whose structure was determined in 1986.[1] It was isolated from the rhizome of *Eleutherine americana* Merr. et Heyne (Iridaceae), a herbal plant from southern China which has been used as a medicine.[1] Hongconin has been shown to exhibit cardioprotective activity against angina pectoris in limited clinical trials.[2]

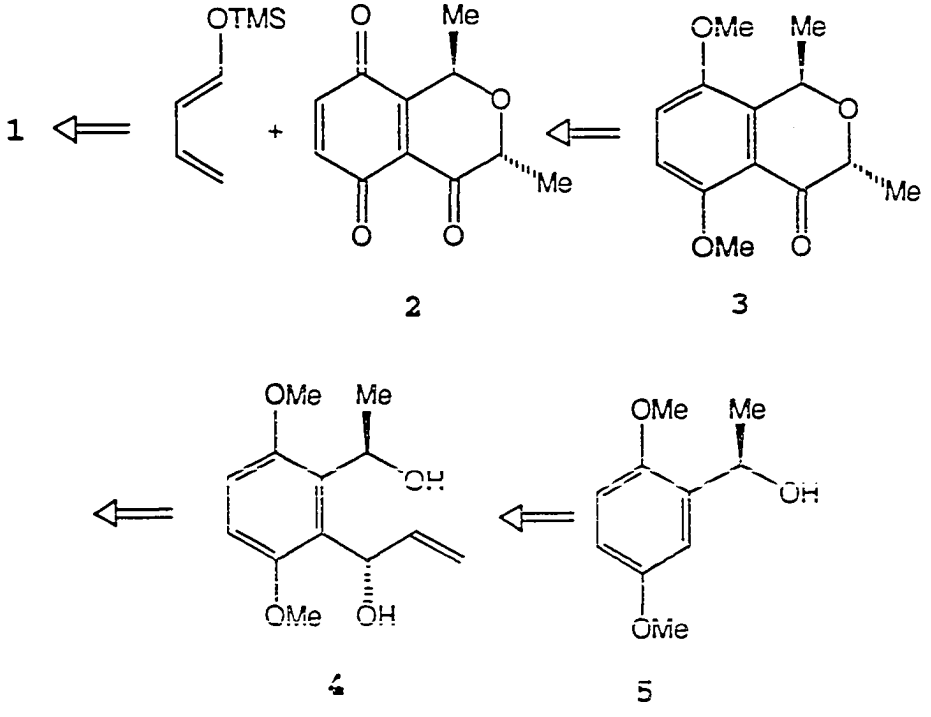


1

The natural occurrence of **1** is low; therefore, the availability of quantities for more definitive testing is likely dependent on the development of a direct synthetic route. As a continuation of our efforts directed toward the development of methodology relevant to the synthesis of quinone natural products, we have addressed the synthesis of hongconin.[3] The following discussion describes the first total synthesis of this novel naphthohydroquinone product.

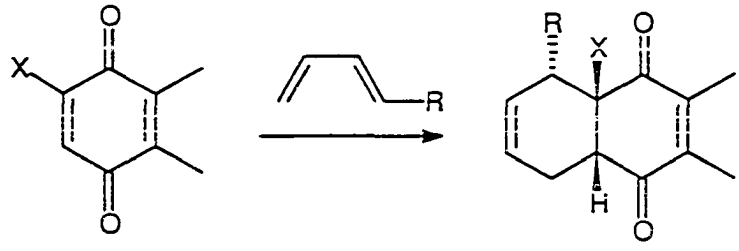
RESULTS AND DISCUSSION*

A retrosynthetic analysis is illustrated below. The synthesis starts from a readily available benzylic alcohol onto which a pyran ring is appended. The benzopyran is converted by oxidation into a quinone which undergoes a Diels-Alder reaction to afford hongconin. Generally, the



regioselective cycloaddition reactions of quinones can be controlled by way of a substituent X such as a halogen or sulfoxide.[4]

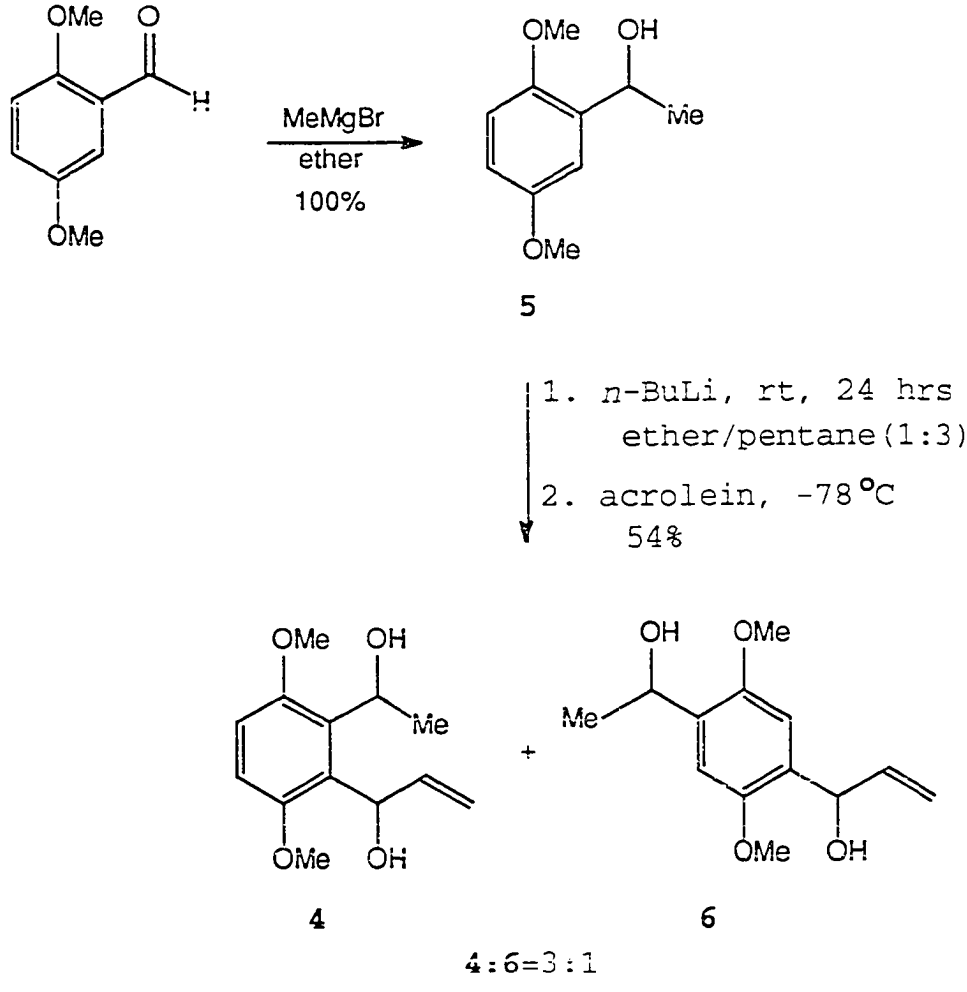
*Calculation was done by Dr. Mark Gordon and Jan H. Jensen



Ref. 4

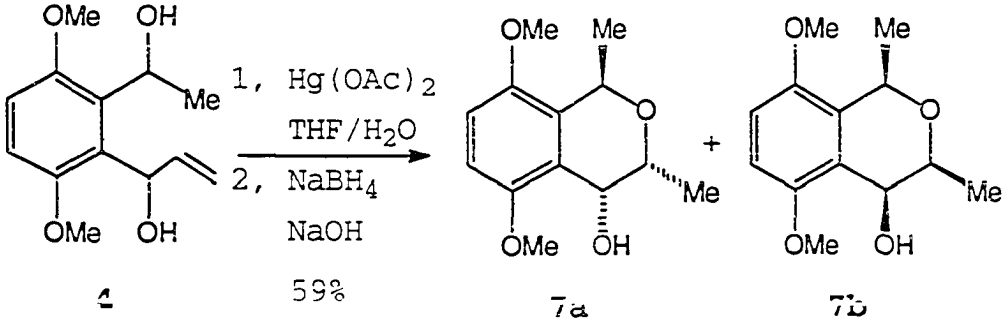
We have developed a new regioselective cycloaddition reaction of quinones which is controlled by a remote substituent such as a lactone.[5b] As part of a program to evaluate the influence of functional groups not directly attached to the atoms undergoing cycloaddition,[5] we decided to determine whether the carbonyl group in the pyranone ring could control the regioselectivity of the Diels-Alder reaction.

The synthesis of benzopyranol 7a is illustrated below. Alcohol **5** was prepared in quantitative yield by the reaction of 2,5-dimethoxybenzaldehyde with methyl magnesium bromide at 0 °C. Alcohol **5** could be converted into its dianion with two equivalents of *n*-butyllithium at ambient temperature for 24 hours in 1:3 ether:pentane. After reaction with acrolein at -78 °C, followed by acidification, an inseparable mixture of diols **4** were isolated in 41% yield. Unexpectedly, an isomeric by-product **6** was also formed in 13% yield.[6]



Interestingly, the reaction of 2,5-dimethoxybenzyl alcohol with two equivalents of *n*-BuLi in THF provided only the intermediate wherein metallation took place ortho to the hydroxymethyl group. Apparently, the lithium alkoxide of the secondary carbinol is a less effective directing group for ortho metallation. This observation might be rationalized by the development of $A^{1,3}$ strain between the ortho-methoxyl group and the benzylic methyl group as the

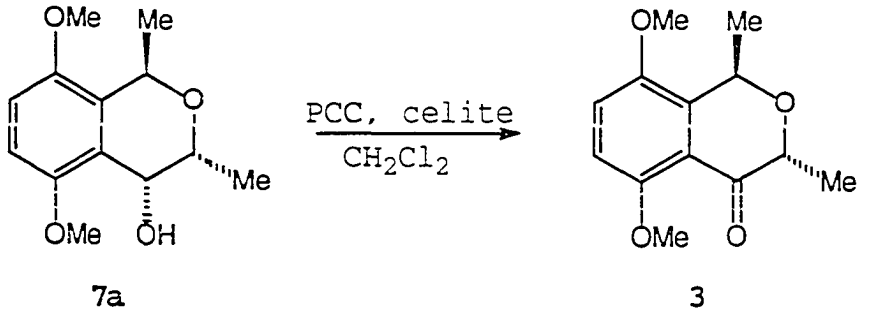
alkoxide adopts the requisite orientation to best direct ortho metallation. The inseparable mixture of diols was treated with mercuric acetate in aqueous THF according to the method of Maruyama.[7] The resulting mercurials were reduced with sodium borohydride to provide a 5:1 ratio of alcohols **7a** and **7b** in 59% isolated yield. The major product **7a** was readily separated from **7b**. The structure of **7a** was tentatively assigned based on NMR coupling constants (particularly the absence of an axial-axial coupling constant) and literature precedent.



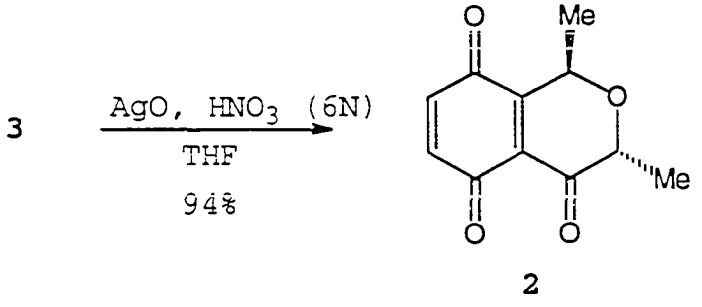
4 7a 7b

7a:7b=5:1

Alcohol **7a** was oxidized to 3 using pyridine chlorochromate (PCC) and Celite in quantitative yield. Ketone **3** was oxidized using the method of Rapoport (AgO/HNO_3)[8] to afford a 94% yield of benzoquinone **2**. Unexpectedly, alcohol **7b**, the minor isomer formed by the

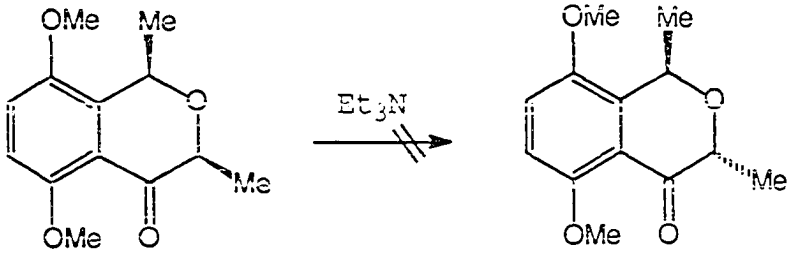


7a 3



2

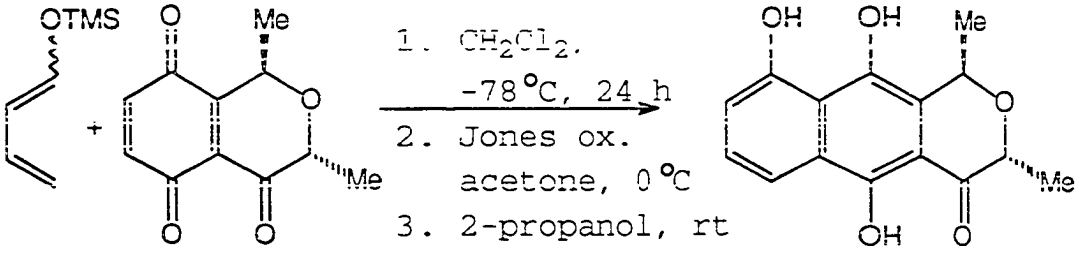
oxymercuration reaction, could not be converted into ketone **3** by oxidation and epimerization. The oxidation of alcohol **7b** with PCC and Celite produced the corresponding ketone, but this ketone resisted epimerization using triethylamine. We had assumed that the pyran ring existed in a chair conformation and that the benzylic methyl group



3

was axial due to $A^{1,3}$ strain. However, RHF/6-31G(d) calculations by Gordon and Jensen suggest that the pyran ring may be in a boat conformation.

With benzoquinone **2** now readily available, we reacted **2** with 1-(trimethylsilyloxy)-1,3-butadiene in methylene chloride at -78 °C for 24 h, followed by treatment of the unpurified adduct with Jones reagent in acetone at 0 °C and quenching the excess Jones reagent with isopropanol. A Diels-Alder reaction could have taken place at either double bond; however, given our previous research results, we expected the reaction to occur at the unsubstituted double bond.[9] We isolated only compound **8** in 51% yield. There were no isomeric by-products or products arising from elimination of the trimethylsilyloxy group.

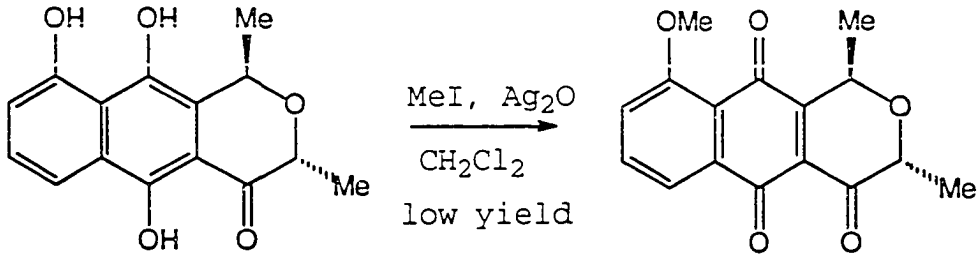


2 51% **8**

The rationale for this remarkably regioselective cycloaddition reaction is not clear. Although the carbonyl group was expected to exert some influence on the

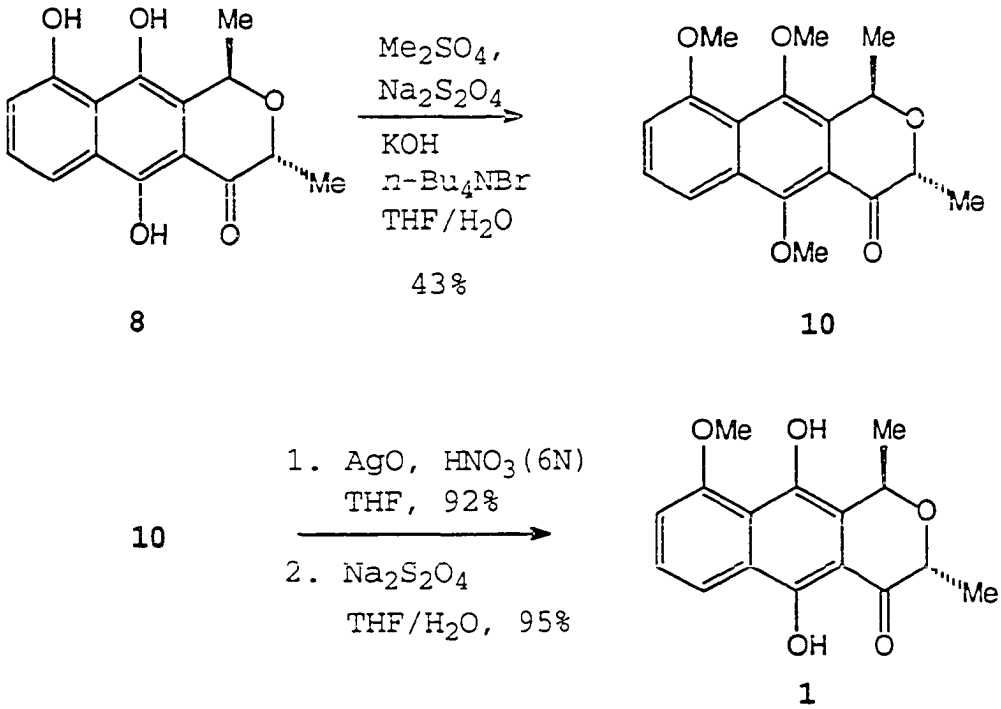
regioselectivity, the magnitude of the influence observed here was unexpected.

Selective methylation would have furnished hongconin in one step by treayment with Ag_2O and CH_3I. Unfortunately, the one step methylation reaction gave only a very low yield and the product was very difficult to purify. In this case, we had to resort to a three-step alternative because direct



8 9

methylation produced a complex mixture of compounds. Methylation using conditions that we had developed for the reductive methylation of hydroxy quinones[10] cleanly generated a triether. Oxidation of the hydroquinone dimethyl ether with AgO followed immediately by reduction with $Na_2S_2O_4$ under neutral conditions provided hongconin (**1**) in 38% overall yield from **7a**. In this reduction, control of pH is very important. The reaction with $Na_2S_2O_4$ under basic conditions afforded only decomposition products.



Earlier studies[11] have successfully used molecular electrostatic potentials to explain the regioselectivity of Diels-Alder reactions, and a similar approach is taken here. All structures were optimized in C_1 symmetry at the AM1[12] level of theory and verified as minima by calculating the Hessian matrix numerically. All structures were then re-optimized at the RHF/6-31G(d)[13] level of theory, but no vibrational analyses were performed at this level of theory due to computational expense. In all cases the changes in structure on going from semiempirical to ab initio theory were small.

All molecular electrostatic potentials[14] (MEPs) were evaluated at the RHF/6-31G* level of theory. Here, a MEP is

defined as the potential felt by a positive test charge due to the molecular charge density, evaluated over a grid of points in a given plane of the molecule. The contour map thus generated identifies relative positively and negatively charged regions of the molecule and can be used, for example, to indicate likely sites for electrophilic and nucleophilic attack.

All calculations were performed with the electronic structure program GAMESS.[15] Most ab initio calculations were performed with a parallel version of GAMESS on a 16-node Intel iPSC/860.

Figure 1 shows two MEPs of **2** evaluated in planes 2 Å below (Figure 1a) and 2 Å above (Figure 1c) and parallel with the dienophile (DP) plane. Figure 1b schematically depicts the orientation of **2** in the MEPs. Both MEPs show a positively charged center region (solid lines) with negatively charged regions (dotted lines) at either side. The plane below the ring shows an almost equal negative charge distribution on either side, due to the quinone oxygens. The plane above the ring shows considerable negative charge on one side, presumably due mostly to the carbonyl group on the pyran ring, but little negative build-up on the other side. Thus, these MEPs indicate that an incoming diene with one electronegative substituent should

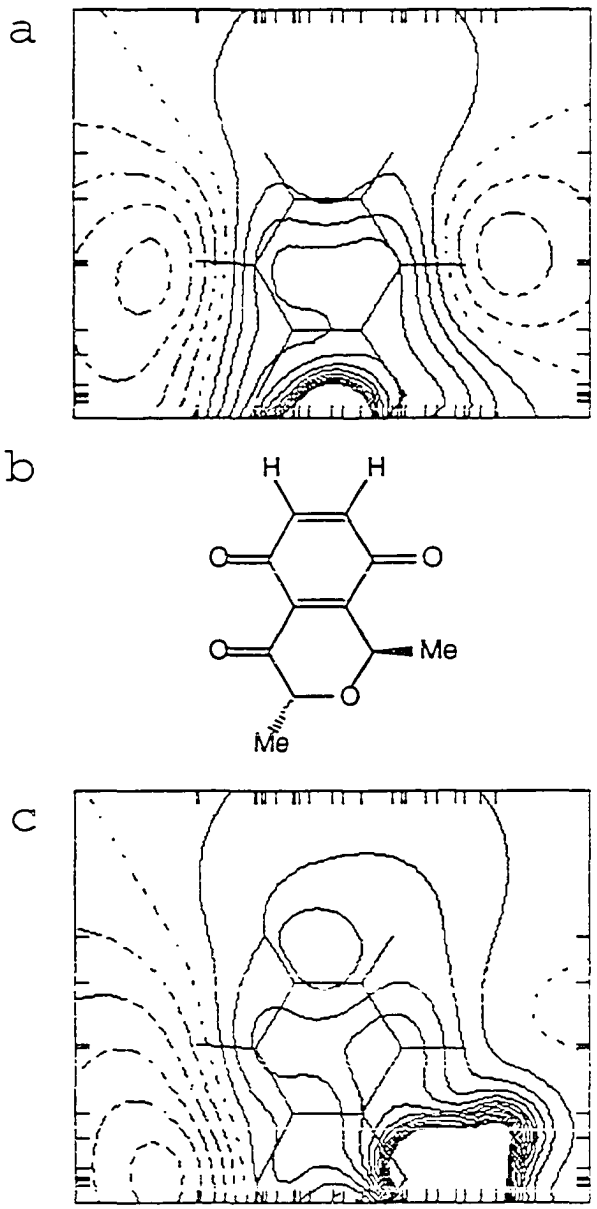


Figure 1 MEPs of **2** evaluated in planes 2 Å below (a) and above (c) the DP plane. The contour spacing is 5 kcal/mol•e. (b) schematic orientation of **2** in the MEPs

prefer to react with **2** from above the DP plane with the substituent oriented away from the carbonyl group.

The observed regioselectivity thus appears to be dictated by the unequal charge distribution and the molecular geometry. The most important geometrical feature of **2** is the non-planar quinone group. Figure 2a shows

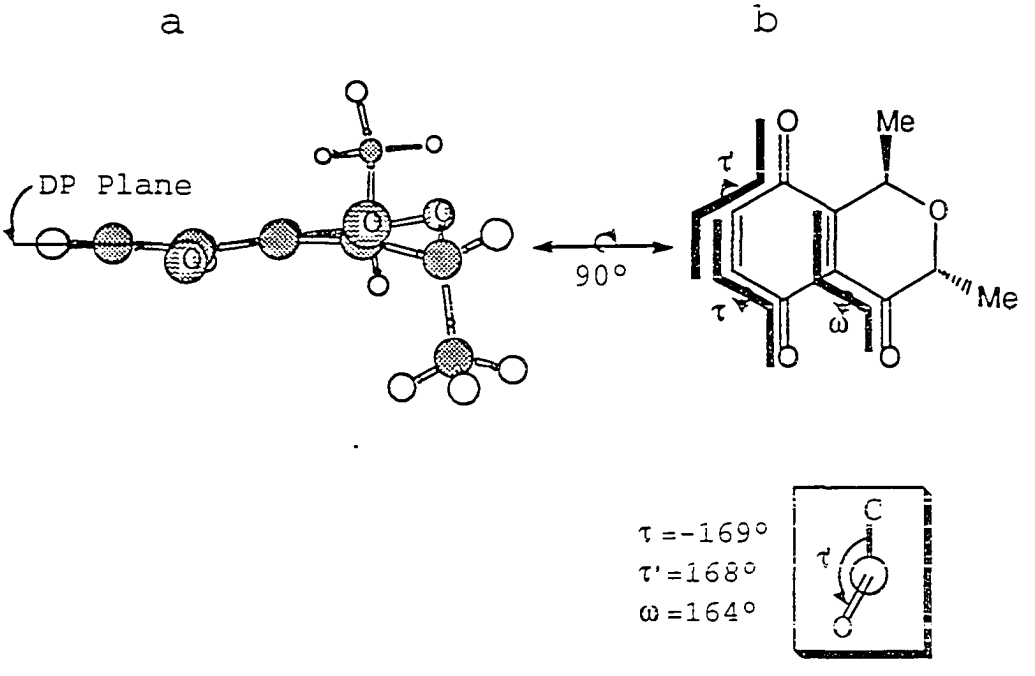


Figure 2 (a) Side view of the AM1 optimized structure of **2** showing the puckering of the quinone ring. (b) Definition of the three dihedral angles used to quantify the deviation from planarity for the quinone oxygens.

that the quinone ring is puckered such that the two quinone oxygens are bent below the DP plane, disfavoring attack from below (Figure 1a). The degree of puckering can be gauged by the dihedral angles between the oxygens and the alkene carbons, defined as τ and τ' in Figure 2; both would be 180° for a planar ring. For **2**, τ and τ' are -169° and 168°, respectively – a roughly 10° deviation from planarity (negative and positive dihedral angles refer to clockwise and counter-clockwise rotation around the center bond, respectively; cf. Figure 2b). A similar parameter, ω in Figure 2b, can be defined for the carbonyl group. For **2**, ω =164° and this 16°-deviation from planarity contributes to the negative contours in the plane 2 Å above the DP plane in Figure 1c.

The cause of the quinone ring puckering may be investigated by monitoring τ, τ', and ω as substituents are added to the pyran ring. The intermediate structures investigated (**11**-**14**) are displayed in Figure 3. Removing all the substituents from **2** (resulting in **11**) results in a flat quinone ring. Adding either the carbonyl **12** or the methyl group **13** to **11** affects only the quinone oxygen that is closest to the respective substituent. In both cases the oxygen has moved 7° out of plane. Note that τ and ω have opposite signs for **13** and **2** because the quinone ring is puckered in opposite directions in the two structures.

Adding both the methyl and carbonyl group to **11** (resulting in **14**) causes a slightly larger distortion from planarity than adding just one of the two, and the dihedral angles in **14** are virtually identical to those in **2**. Therefore, it appears that the two pyran ring substituents neighboring the quinone ring induce the quinone ring-puckering that contributes to the regioselectivity.

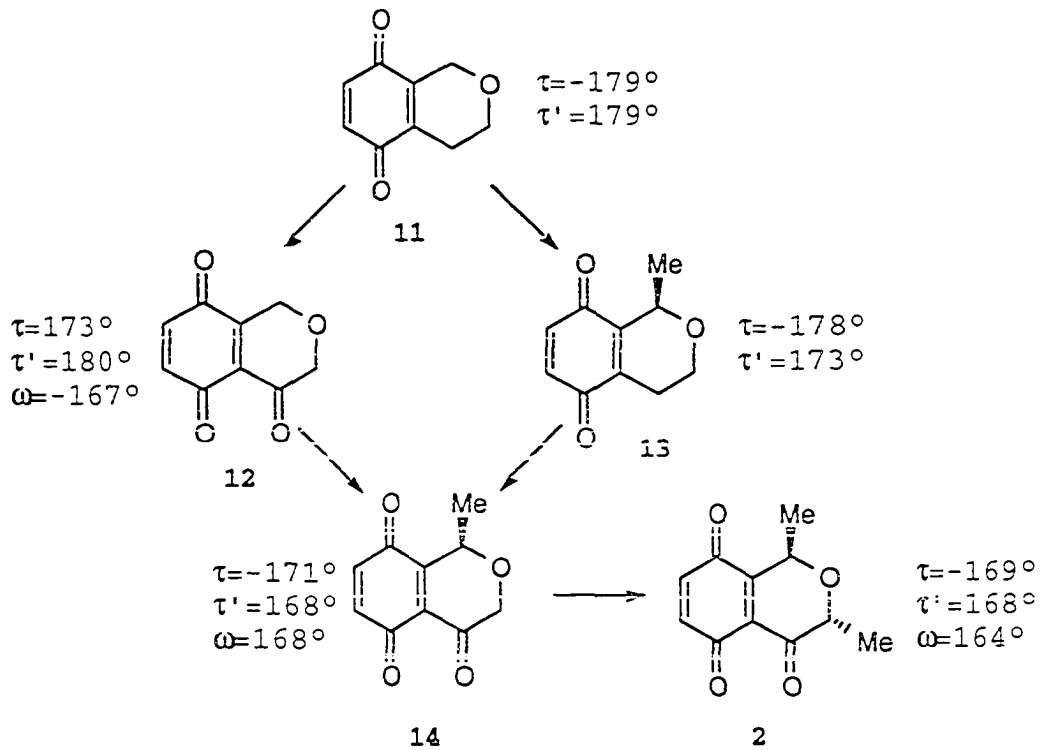


Figure 3 RHF/6-31G* values for τ, τ' and ω as a function of pyran ring substituent

CONCLUSION

A total synthesis of racemic hongconin has been completed in eight steps from alcohol **5**. Our synthetic route features a benzylic alcohol metallation and a remarkably regioselective Diels-Alder reaction. This synthetic route is flexible and direct. Additional biological evaluation of this interesting but rare natural product will soon be forthcoming.

EXPERIMENTAL

Unless otherwise noted, materials were obtained from commercial suppliers and were used without purification. Diethyl ether and tetrahydrofuran (THF) were distilled from sodium benzophenone ketyl. Benzene was distilled from lithium aluminum hydride. Methylene chloride and acetonitrile were purified by distillation from calcium hydride. Apparatus for experiments requiring anhydrous conditions was flame-dried under a stream of argon or dried in a 150 °C oven for 12 h and cooled under a stream of argon or in a desiccator. Flash chromatography was performed on EM Science Kieselgel 60 (mesh 230-400). Thin layer chromatography was performed using Merck TLC plates (silica gel 60) with a thickness of 0.25 mm. The solvent system was a suitable mixture of hexane (H) and ethyl acetate (EA) unless otherwise noted. The abbreviation sg represents silica gel. Infrared spectra were obtained on a Bio-Rad FTS-7 spectrophotometer and are reported in cm^{-1}. Proton nuclear magnetic resonance spectra (300 MHz) were obtained using a Nicolet Magnetic Corporation NT-300 spectrometer. All chemical shifts are reported in δ relative to tetramethylsilane as a internal standard. Splitting patterns are designated as s (singlet), d (doublet), t (triplet), q (quartet), dd (doublet of doublets), dt (doublet of

triplets), ABq (AB quartet), and m (multiplet); a br prefix indicates a broadened pattern. Carbon-13 NMR spectra were obtained on the Nicolet Magnetic Corporation NT-300 spectrometer and were reported in δ relative to $CDCl_3$ (77.00 ppm. High resolution mass spectra were obtained on a Kratos model MS-50 spectrometer. Low resolution mass spectra were obtained on a Finnegan 4023 mass spectrometer. Melting points were determined on a Fisher-Johns melting point apparatus and are uncorrected. Optical rotations were obtained using a JASCO DIP-370 digital polarimeter. The purity of all title compounds was determined to be >95% by 300 MHz proton NMR and/or elemental analysis.

3,4-Dihydro-5,8-dimethoxy-1,3-dimethyl-1H-2-benzopyran-4-ols (7a) and (7b). To a solution of alcohol **5** (9.6 g, 53.0 mmol) in ether:pentane (1:3, 400 mL) at 0 °C was added n-butyllithium in hexane (48.6 mL, 110 mmol) dropwise with vigorous stirring. The solution was allowed to warm to rt and was stirred for 24 h. The solution was then cooled to -78 °C and acrolein (7.82 mL, 62.6 mmol) was added. After the reaction had stirred for 2 h at -78 °C, it was quenched with saturated ammonium chloride solution and extracted three times with ethyl acetate. The organic layers were dried with sodium sulfate and concentrated in vacuo. The residue was purified by sgc using 4:1 H:EA to afford 5.1 g

(41% yield) of an inseparable mixture of diols, 4.1 g of starting material and an unidentified compound (see reference 6).

To a solution of the inseparable mixture of diols **4** and **6** (2.87 g, 12.0 mmol) in THF-H_2O (2:1, 150 mL) was added mercuric acetate (4.0 g, 12.6 mmol) and the solution was stirred for 5 h at rt. The reduction of the resulting mercurial intermediate was achieved by adding 0.23 g of $NaBH_4$ dissolved in 24 mL of 2 M NaOH. The mixture was allowed to stir for 10 h. The solution was then neutralized with 3 N HCl and extracted with ether. The organic layer was washed with brine and dried over Na_2SO_4. The solvent was removed *in vacuo* and the residue was purified by sgc (H:EA=4:1) to afford 1.4 g (49% yield) of **7a** and 0.28 g (10% yield) of **7b**. Both compounds were viscous light yellow oils.

7a. NMR ($CDCl_3$) δ 1.39 (d, J = 6.3 Hz, 3 H), 1.48 (d, J = 6.6 Hz, 3 H), 2.09 (d, J = 7.2 Hz, 1 H), 3.77 (s, 3 H), 3.84 (s, 3 H), 4.03-4.10 (m, 1 H), 4.52 (dd, J = 7.5, 1.8 Hz, 1 H), 5.08 (q, J = 6.6 Hz, 1 H), 6.73 (s, 2 H); IR ($CDCl_3$) 3578, 3423, 1259, 980 cm^{-1}; MS: m/z 77, 91, 121, 133, 161, 179, 194, 205, 220, 238; HRMS: m/z for $C_{13}H_{18}O_4$ calcd. 238.1205, measured 238.1204; CMR ($CDCl_3$) δ 16.8, 17.9, 55.4, 55.7, 62.4, 66.0, 68.4, 108.4, 109.5, 125.4, 128.8, 149.0, 151.2; TLC (H:EA = 2:1) R_f = 0.40.

7b. NMR ($CDCl_3$) δ 1.39 (d, J = 6.6 Hz, 3 H), 1.58 (d, J = 6.3 Hz, 3 H), 2.02 (d, J = 9.0 Hz, 1 H), 3.63-3.69 (m, 1 H), 3.77 (s, 3 H), 3.84 (s, 3 H), 4.57 (d, J = 9.0 Hz, 1 H), 4.92 (q, J = 6.3 Hz, 1 H), 6.72-6.78 (m, 2 H); IR ($CDCl_3$) 3578, 3423, 1380, 939 cm^{-1}; MS: m/z 77, 91, 103, 121, 133, 161, 179, 194, 205, 223, 238; HRMS: m/z for $C_{13}H_{18}O_4$ calcd. 238.1205, measured 238.1204; CMR ($CDCl_3$) δ 16.8, 17.9, 55.4, 55.7, 62.4, 66.0, 68.4, 108.4, 109.5, 125.4, 128.8, 149.0, 151.2; TLC (H:EA = 2:1) R_f = 0.44.

3,4-Dihydro-5,8-dimethoxy-1,3-dimethyl-1H-2-benzopyran-4-one (3). To a suspension of PCC (0.72 g, 3.74 mmol) and Celite (1.0 g) in CH_2Cl_2 (10 mL) at 0 °C was added **7a** (0.20 g, 0.84 mmol) in 10 mL of CH_2Cl_2. The mixture was warmed to rt and stirred overnight. The solvent was removed *in vacuo* and the residue was purified by sgc (H:EA=2:1) to afford 198 mg (100% yield) of **3** an oil. ^1H NMR ($CDCl_3$) δ 1.47 (d, J = 6.6 Hz, 3 H), 1.55 (d, J = 6.6 Hz, 3 H), 3.82 (s, 3 H), 3.88 (s, 3 H), 4.54 (q, J = 6.6 Hz, 1 H), 5.31 (q, J = 6.6 Hz, 1 H), 6.94 (ABq, 2 H); IR ($CDCl_3$) 1683, 1435, 1266, 990 cm^{-1}; MS: m/z 77, 91, 121, 134, 149, 163, 177, 192, 221, 236; HRMS: m/z for $C_{13}H_{16}O_4$ calcd. 236.1048, measured 236.1047; CMR ($CDCl_3$) δ 17.4, 17.7, 55.8, 56.1, 66.7, 71.3, 110.6, 116.6, 117.7, 136.9, 147.4, 153.6, 195.8; TLC (H:EA = 2:1) R_f = 0.42.

3,4,5,8-Tetrahydro-1,3-dimethyl-1H-2-benzopyran-4,5,8-trione (2). To a suspension of **3** (138 mg, 0.585 mmol) and AgO (363 mg, 2.92 mmol) in 15 mL of THF at rt was added 0.59 mL of 6 N HNO_3. After 1 h, the reaction was quenched by the addition of 3 mL of water. The mixture was extracted with ether (3x30 mL). The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. The crude product was purified by sgc (H:EA=2:1) to afford 114 mg (94% yield) of **2**. ^1H NMR ($CDCl_3$) δ 1.42 (d, J = 6.6 Hz, 3 H), 1.60 (d, J = 6.9 Hz, 3 H), 4.45 (q, J = 6.6 Hz, 1 H), 5.03 (q, J = 6.9 Hz, 1 H), 6.79 (ABq, 2 H); IR ($CDCl_3$) 1714, 1666, 1286 cm^{-1}; MS: m/z 78, 106, 134, 162, 206; HRMS: m/z for $C_{11}H_{10}O_4$ calcd. 206.0579, measured 206.0583; CMR ($CDCl_3$) δ 16.3, 17.3, 66.1, 71.2, 124.3, 135.5, 136.8, 152.8, 183.4, 187.4, 194.4; TLC (H:EA = 3:1) R_f = 0.40.

3,4-Dihydro-5,9,10-trihydroxy-1,3-dimethyl-1H-naphtho [2,3-c]pyran-4-one (8). To a solution of **2** (720 mg, 3.5 mmol) in CH_2Cl_2 (25 mL) at -78 °C was added dropwise 1-(trimethylsilyloxy)-1,3- butadiene (2.45 mL, 14.0 mmol). The mixture was stirred at -78 °C for 24 h. After the solvent was removed *in vacuo*, the residue was dissolved in 10 mL of acetone and 2.7 M Jones reagent (3.1 mL, 8.39 mL) was added at 0 °C. The reaction was then quenched with isopropanol (5 mL) and stirred for 5 h at rt. The mixture

was filtered and solvent was removed *in vacuo*. The residue was partitioned between saturated ammonium chloride solution (10 mL) and ether (3 x 50 mL). The organic extracts were washed with brine and dried over sodium sulfate. The solvent was concentrated *in vacuo* and the residue was purified by sgc (H:EA=5:1) to afford 490 mg (51% yield) of **8**. ^{1}H NMR (CD_3OD) δ 1.29 (d, J = 6.6 Hz, 3 H), 1.43 (d, J = 6.6 Hz, 3 H), 4.50 (q, J = 6.6 Hz, 1 H), 5.20 (q, J = 6.6 Hz, 3 H), 6.76 (d, J = 7.2 Hz, 1 H), 7.07 (t, J = 8.2 Hz, 3 H), 7.61 (d, J = 8.4 Hz, 1 H), 12.63 (s, 1 H); IR ($CDCl_3$) 1647, 1614,1291,921 cm^{-1}; MS: m/z 121, 172, 203, 213, 228, 241, 259, 274; HRMS: m/z for $C_{15}H_{14}O_5$ calcd. 274.0841, measured 274.0835; CMR (CD_3OD) δ 16.4, 17.6, 68.6, 70.5, 108.2, 114.3, 117.2, 120.2, 120.3, 126.9, 127.1, 141.1, 154.4, 155.3, 203.8; TLC (H:EA = 2:1) R_f = 0.37.

3,4-Dihydro-5,9,10-trimethoxy-1,3-dimethyl-1H-naphtho[2,3-c]pyran-4-one (10). To a solution of **8** (100mg, 0.365 mmol) and tetra-*n*-butylammonium bromide (30 mg, 0.091 mmol) in 5 mL of THF and 2 mL of water was added 2 mL of aqueous sodium dithionite (640 mg, 3.65 mmol). After 15 minutes at rt, 1 mL of aqueous KOH (1.02 g, 18.3 mmol) was added. After 2 minutes, 4 mL of dimethyl sulfate was added and the mixture was stirred for 12 h. The crude product was extracted by

partitioning between water (5 mL) and ether (3 x 20 mL). The organic layer was mixed with 5 mL of triethylamine to remove any remaining dimethyl sulfate. The sovent was concentrated *in vacuo* . The crude product was purified by sgc (H:EA=6:1) to afford 50 mg (43% yield) of **10**. ^{1}H NMR ($CDCl_3$) δ 1.51 (d, *J* = 6.6 Hz, 3 H), 1.68 (d, *J* = 6.6 Hz, 3 H), 3.85 (s, 3 H), 3.99 (s, 3 H), 4.03 (s, 3 H), 4.59 (q, *J* = 6.6 Hz, 1 H), 5.50 (q, *J* = 6.6 Hz, 1 H), 7.02 (d, *J* = 7.8 Hz, 1 H), 7.44 (t, *J* = 8.2 Hz, 1 H), 7.96 (d, *J* = 8.4 Hz, 1 H); IR ($CDCl_3$) 1689, 1611, 1583, 1263, 1100, 900 cm^{-1}; MS: m/z 91, 115, 136, 155, 171, 185, 199, 229, 257, 272, 301, 316; HRMS: m/z for $C_{18}H_{20}O_5$ calcd. 316.1311, measured 316.1310; CMR ($CDCl_3$) d 17.8, 19.5, 58.2, 62.4, 62.9, 67.6, 71.7, 109.0, 117.0, 117.6, 123.4, 126.5, 131.4, 133.6, 146.2, 154.7, 155.6, 196.7; TLC (H:EA = 2:1) R_f = 0.52.

Hongconin (1). To a suspension of **10** (46 mg, 0.146 mmol) and AgO (72 mg, 0.582 mmol) in 3 mL of THF at rt was added 0.15 mL of 6N HNO_3. After 1 h, the reaction was quenched by the addition of 3 mL of water. The mixture was extracted with ether (3x10 mL) and the organic layer was dried over Na_2SO_4 and was concentrated *in vacuo*. The crude product was then dissolved in THF-H_2O (1 mL: 0.6 mL) and cooled to 0 °C. This solution was treated with $Na_2S_2O_4$ (26 mg, 0.15 mmol) for 15 min. The mixture was extracted with ether and the

organic layer was washed with brine and dried over Na_2SO_4. The solvent was removed *in vacuo* and the crude product was purified by sgc to afford 37 mg (88% yield) of **1**. ^1H NMR ($CDCl_3$) δ 1.53 (d, *J* = 6.6 Hz, 3 H), 1.64 (d, *J* = 6.6 Hz, 3 H), 4.07 (s, 3 H), 4.69 (q, *J* = 6.6 Hz, 1 H), 5.49 (q, *J* = 6.6 Hz, 1 H), 7.01 (d, *J* = 7.5 Hz, 1 H), 7.38 (t, *J* = 8.1 Hz, 1 H), 8.05 (d, *J* = 8.7 Hz, 1 H), 8.97 (s, 1 H), 12.82 (s, 1 H); IR ($CDCl_3$) 3422, 1646, 1610, 1579, 1458, 1387, 1290, 1253, 1233, 1102, 1053, 924, 979, 760 cm^{-1}; CMR ($CDCl_3$) δ 16.3, 17.4, 58.4, 67.4, 69.4, 107.8, 109.1, 118.0, 119.5, 120.9, 125.4, 125.9, 139.4, 154.3, 155.6, 202.8; MS: m/z 91, 173, 227, 245, 273, 288; HRMS: m/z for $C_{16}H_{16}O_5$ calcd. 288.0998, measured 288.0990; TLC (H:EA = 2:1) R_f = 0.61.

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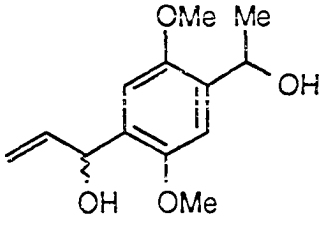
6. The exact structure is not clear. We believe that it has the structure shown below:



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GENERAL SUMMARY

In the first part of this research, the regioselectivity of Diels-Alder reactions of quinones controlled by remote substituents was discovered. By using this new methodology, several pyranonaphthoquinone natural products, such as kalafungin, frenolicin B, α,β-epoxyfrenolicin B and their analogs, were synthesized in only 6-8 steps from simple commercially available starting materials. The second part of the research dealt with the total synthesis of hongconin, a novel naphthohydroquinone natural product. Our synthetic routes are flexible and direct. The approach to the control of regioselectivity described herein should be applicable to many other natural product systems.

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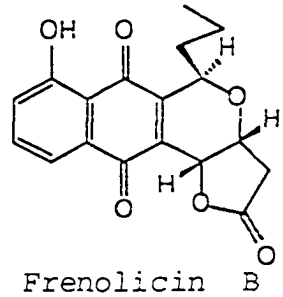
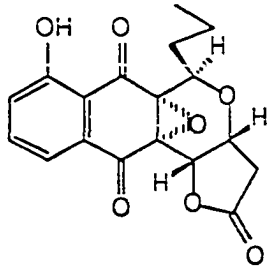
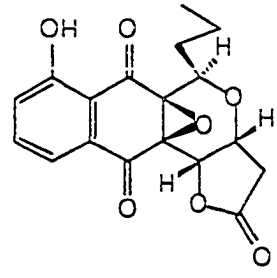
APPENDIX A: LIST OF NATURAL PRODUCTS AND THEIR ANALOGS SYNTHESIZED IN THIS THESIS



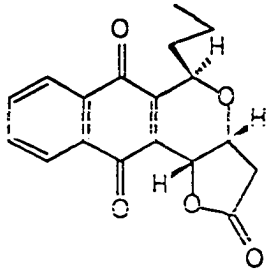
Frenolicin B



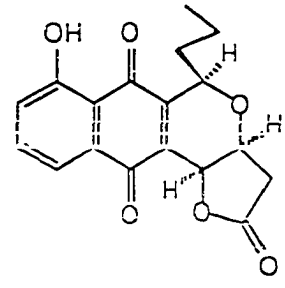
(α)-Epoxyfrenolicin B



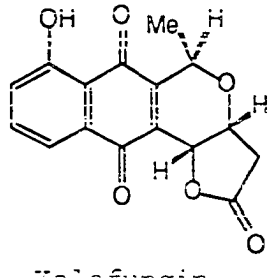
(β)-Epoxyfrenolicin B



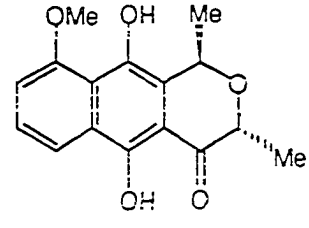
7-Deoxyfrenolicin B



5-Epi-frenolicin B



Kalafungin
Nanaomycin D



Hongconin

APPENDIX B: SINGLE-CRYSTAL X-RAY STRUCTURE OF FRENOLICIN B

(1) Crystal Data

Formula	C18H16O6
Color; Habit	Orange, plate
Crystal size (mm)	0.45 X 0.20 X 0.10
Crystal system	Triclinic
Space group	P1
Unit cell dimensions	a = 7.100(2) Å
	b = 15.556(4) Å
	c = 16.074(6) Å
	α = 118.90(2)°
	β = 92.02(3)°
	γ = 97.35(2)°
Volume	2026.9(4) Å^3
Z	4
Formula weight	327.8
Density (calc.)	1.421 Mg/m^3
Absorption coefficient	0.902 mm^{-1}
F (000)	686

(2) Crystal Structure of Frenolicin B