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Synthetic approaches to aromatic antitumor agents and antibiotics

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SYNTHETIC APPROACHES TO AROMATIC ANTITUMOR AGENTS AND ANTIBIOTICS

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Synthetic approaches to aromatic antitumor agents and antibiotics

by

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DEDICATION

This dissertation is dedicated to my late grandfathers, Mr. Melvin Campbell and Mr. Julias "Al" Walling. Although neither of these men had the opportunity for higher education, their outstanding wisdom and qualities have and will continue to play an important role in my life. My great love and respect for them will never be forgotten.

GENERAL INTRODUCTION

When a synthesis of a complex natural product or class of natural products is planned, many considerations are brought to the fore. Aside from the desire to accomplish an esthetically pleasing synthesis, the reactions used must proceed in high yield, and guarantee a high degree of regio- and stereoselectivity. If the reactions employed or discovered are operationally convenient, then another synthetic goal has been achieved. It was the purpose of this research to discover and apply novel synthetic strategies to aromatic antitumor antibiotics. Part I describes a facile entry to the carbon framework of olivin. Part II describes an efficient and convenient preparation of the aromatic subunit of alkavinone. Finally, Part III details the total synthesis of two important members of the pyranonaphthoquinone class of antibiotics.

Explanation of Thesis Format

This thesis is written so that each section can be regarded as a separate article in publishable form. Therefore, the numbering of the figures, schemes, tables, and references is independent in each division.

PART I: A SYNTHETIC APPROACH TO OLIVIN

INTRODUCTION

Olivin and chromomycinone are structural subunits of a growing class of potent antitumor antibiotics collectively known as the aureolic acids. At the time this work was initiated, no total synthesis of these interesting natural products had been reported. This manuscript will detail the results of a program directed toward the total synthesis of olivin in optically active form.

HISTORICAL

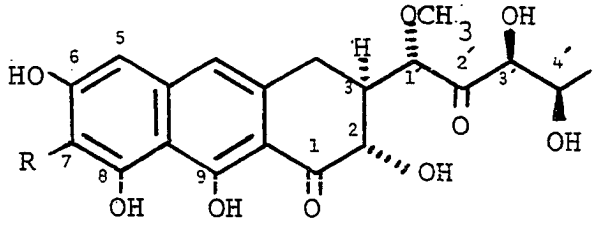
The first member of the aureolic acid class of antitumor antibiotics was isolated at the Abbott Laboratories in 1953 from an unknown Streptomyces species (1). Microbiological testing indicated activity against Gram(+)bacteria in vitro. Its high toxicity precluded its use as a potential antibacterial agent (1b). The compound was named aureolic acid due to its acidic properties. Aureolic acid was later discovered as LA-7017 by workers at Lepetit Laboratories (1c), and as mithramycin by workers at Pfizer Laboratories (1d). It was not until 1968 that LA-7017 and mithramycin were correlated with aureolic acid (1e).

Since the initial isolation of members of the aureolic acid class in 1953, two other subclasses of aureolic acid antibiotics have been isolated and microbiologically characterized. The chromomycins were isolated from Streptomyces griseusis by Shibata et al. in 1960 (2). Later, the discovery and isolation of the olivomycins as NSC A-649 was accomplished by workers at the Bristol Laboratories. The antibiotic was found to be active against Gram(+)bacteria, and several animal tumors including the Ridgway osteogenic sarcoma, the Harding-Passey melanoma in mice, and the Walker carcinosarcoma in rats (3).

Many of the aureolic acid antibiotics have now evolved into clinically useful drugs for the treatment of human

cancers. Mithramycin (aureolic acid) has been approved for use in the treatment of testicular cancers (4). The medicinal and biochemical aspects of this class of interesting drugs have been the subject of several reviews (5-10). The most important aspects of structure will be summarized here and, along with more recent information, the studies relating to the mode of DNA binding, and syntheses of the polysaccharide and aglycone subunits.

The structures of the three subclasses of aureolic acid antibiotics; the aureolic acids, the chromomycins, and the olivomycins, are based in part upon two aglycones, olivin (11) (1a) and chromomycinone (12) (1b).



1a R= H: olivin
1b R= CH_3: chromomycinone

The aureolic acids and the chromomycins have in common the aglycone chromomycinone, while the olivomycins contain the tetrahydroanthracene subunit known as olivin. The structures of the two aglycones are nearly identical except for the methyl group at position 7.

The above aglycones are linked at both the phenolic 6- and hydroxylic 2-positions by dideoxypyranose sugar residues. The C-6 position is most often linked with a disaccharide residue, while a trisaccharide is the common substituent at the C-2 position. The structure of one member of each subclass of aureolic acids has recently been revised. Thiem and Meyer have used a combination of detailed high field ^{13}C and ^{1}H NMR analyses to arrive at the nature of the interglycosidic linkages of chromomycin A_3 (13) and olivomycin A (14). Their initial studies of the interglycosidic linkages of mithramycin were conclusive at all but one linkage (14). Fortunately, a combination of synthetic and spectroscopic techniques led to the assignment of the previously unknown linkage (15).

The complete structure of olivomycin A (2) is shown below. The compositions of some selected aureolic acid antibiotics are provided in Table 1. Additionally, the structures of the dideoxy sugars are shown in figure 1.

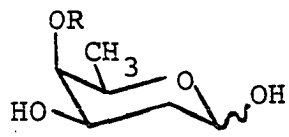
It has long been known that chromomycin A_3, mithramycin, and olivomycin A complex with double-stranded DNA (16). Each inhibits DNA-dependent RNA synthesis by complexing with DNA. Unique to this class of antibiotics is the fact that Mg(II) or another divalent metal cation is necessary for complexation to occur (17). Furthermore, intercalation of the aglycone moieties with the purine and pyrimidine bases of DNA is not the important binding interaction (18). This is surprising in

Table 1. Compositions of some selected aureolic acid antibiotics

Compound	Aglycone	Sugars[a]
mithramycin	chromomycinone	oliose, olivose, olivose, olivose, D-mycarose
olivomycin A	olivin	acetyloliose, divomose, olivose, olivose, 4-isobutyrylolivomycose
olivomycin B	olivin	acetyloliose, olivomose, olivose, divose, 4-acetylolivomycose
olivomycin C	olivin	oliose, olivomose, olivose, olivose, 4-isobutyrylolivomycose
olivomycin D[b]	olivin	acetyloliose, olivomose, olivose, olivose
chromomycin A_3	chromomycinone	acetyloliose, olivomose, olivose, olivose, 4-isobutyrylolivomycose

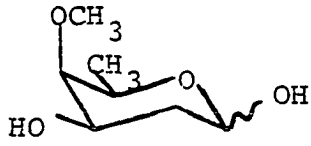
[a]Named in the order A, B, C, D, E as shown in structure 2 for olivomycin A.

[b]Olivomycin D contains only four dideoxy sugars.

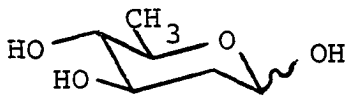


R= H: D-oliose

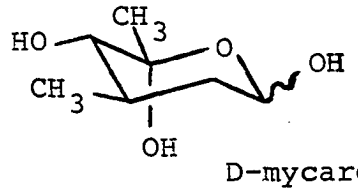
R= $COCH_3$: D-acetyloliose



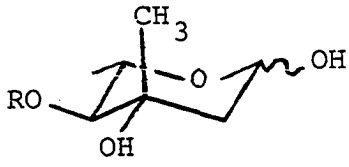
D-olivomose



D-olivose



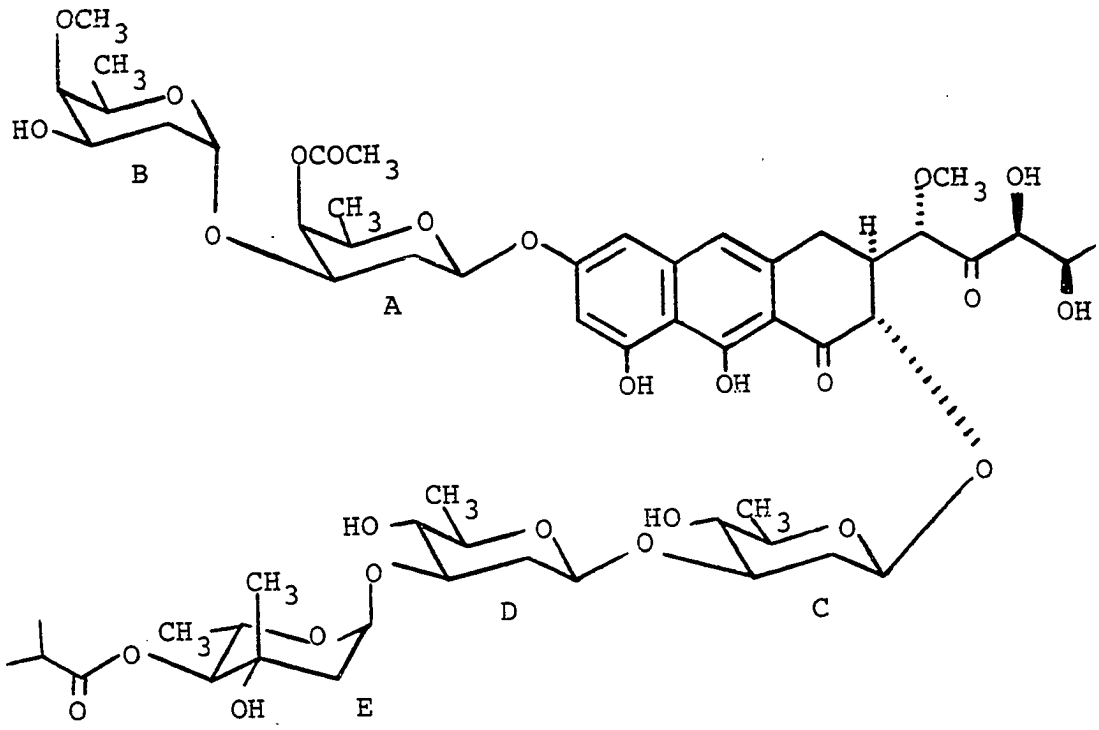
D-mycarose



R= $COCH_3$: L-4-acetylolivomycose

R= $COCH(CH_3)_2$: L-4-isobutyrlolivomycose

Figure 1. Structures of the dideoxy sugars commonly found in the aureolic acid group

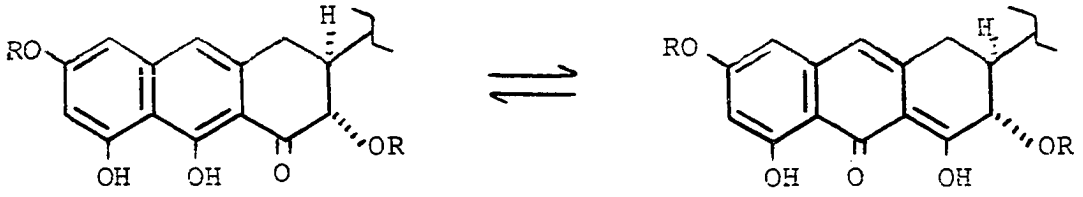


2 olivomycin A

light of the structural similarities with the anthracyclines which are known DNA intercalating agents.

In a recent spectroscopic study of the mechanism of complexation of olivomycin and Mg(II), it was determined that complexation was a two step process. In the first step, Mg(II) binds to the A-ring keto-oxygen. In the subsequent step, the olivomycin-Mg(II) complex collapses to a stable, more compact conformation (19). In the presence of DNA, the first step is followed by the binding of the O-acyl group of the 4-isobutyrylolivomycose residue and hydroxyl groups of olivomose and 4-isobutyrylolivomycose to Mg(II). The more

compact conformation of olivomycin-Mg(II) facilitates its binding to the narrow groove of DNA (20). A similar study suggests that two tautomeric forms of olivomycin A may play a role in the pharmacokinetics of the aureolic acid group (21).



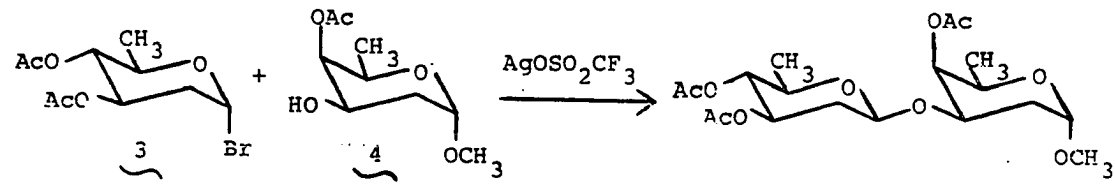
Based on kinetic evidence, a group of Soviet workers postulated that a major complexation interaction occurs between the sugar-phosphate backbone of DNA and the glycoside residues of olivomycin. It was also suggested that a pronounced binding specificity of olivomycin for dG•dC rich regions of DNA was due to hydrogen bonding between a guanine 2-amino group and the phenolic olivin ring system (22).

Van Dyke and Dervan have recently reported the base sequence binding preferences of chromomycin A_3, mithramycin, and olivomycin A. Utilizing a combination of (methidium-propyl-EDTA)iron(II) cleavage of drug protected DNA restriction fragments (23) and Maxam-Gilbert sequencing methods, the preferred sites on a 70 base sequence of DNA were determined. Apparently, binding sites are a minimum of three base pairs in size, and must contain at least two contiguous and complementary dG•dC base pairs on double-stranded DNA. Additionally, olivomycin A and chromomycin A_3, which share

common hexopyranose sugars, were remarkably similar in binding specificity (24).

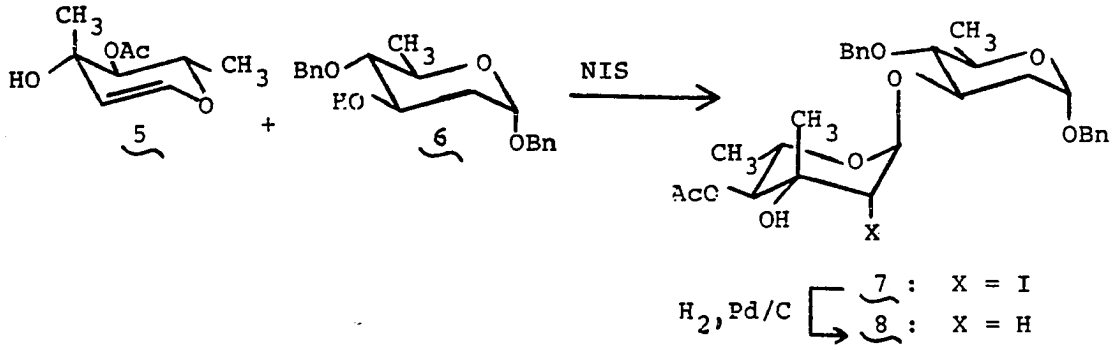
The fact that no accurate model of antitumor action yet exists has not hindered synthetic efforts in the area. Synthetic endeavors along two fronts, the polysaccharide units and the aglycones, have been in progress since 1960. The syntheses of all of the monosaccharides have now been completed (25), and the saccharide synthesis program has been reviewed through 1977 (5).

The synthesis of the disaccharide units has been largely due to the work of Thiem. The preparation of the B-A fragment of mithramycin was accomplished by silver(I) mediated condensation of the glycone components 3 and 4 (26).

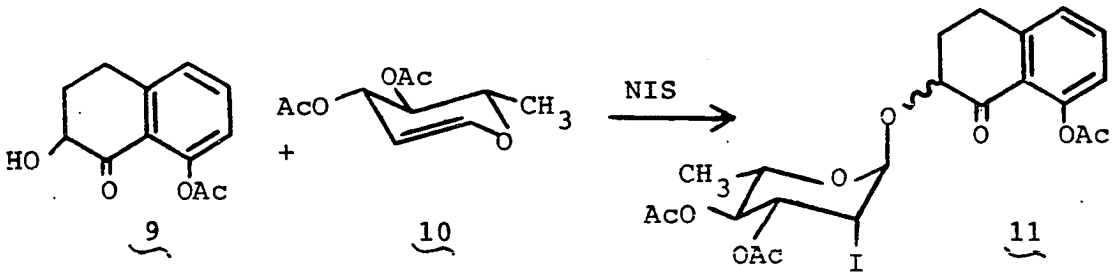


A different method was employed to construct the E-D disaccharide unit of chromomycin A_3. Condensation of glycol 5 and 6 through the use of N-iodosuccinimide (NIS) provided 7 which was partially hydrogenated to afford 8 (27).

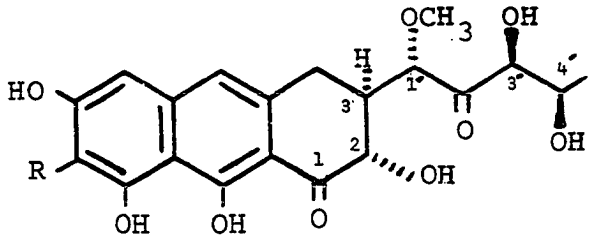
The synthesis of the B-A disaccharides and D-C subunits of chromomycin A_3 and olivomycin A (28, 29) and the E-D-C subunit of olivomycin A (30) parallel the work provided above. Model



system studies have also been done by Thiem and coworkers which clearly indicate that coupling of saccharide units to the olivin or chromomycinone aglycones is feasible. Thus, the tetralone 9, when reacted with 10 and NIS, produces the model tetralone olivoside 11 (31).



While the syntheses of the various oligosaccharide subunits of the aureolic acid class have been rather straightforward, comparable success in the synthesis of the aglycones chromomycinone and olivin has not been realized. The aglycones of the aureolic acid group present interesting challenges for the natural products chemist.

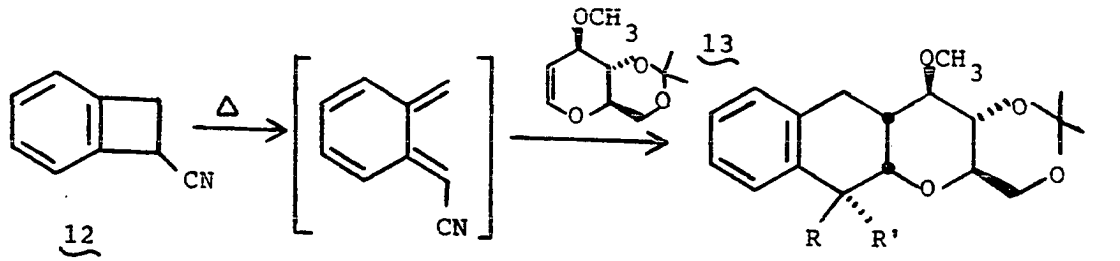


1a R = H: olivin

1b R = CH_3: chromomycinone

By consideration of the structures of 1a and 1b, various regiochemical and stereochemical issues become apparent. Of these, the relative stereochemistry at C-3, C-2, and C-1' and the necessity for regiocontrol in the construction of the CBA ring system pose special problems. To this date, the Diels-Alder cycloaddition (32) and anionic reactions have been used to address these problems of regio- and stereocontrol.

Synthetic approaches based on Diels-Alder methodology were initiated by Franck and John (33). In a model system study, cyanobenzocyclobutane 12 and glycol 13 were heated to afford 14 and 15 via the o-quinone methide of 12.



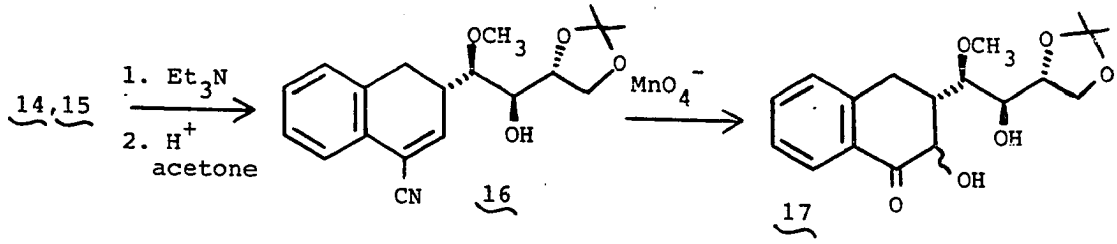
12

13

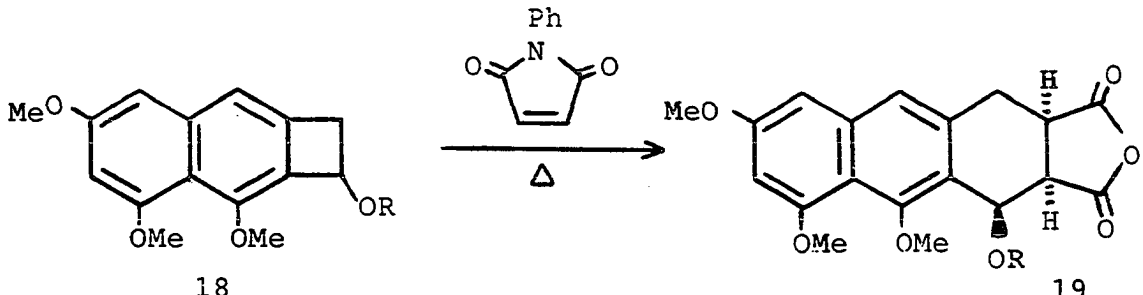
14 R' = CN, R = H

15 R' = H, R = CN

While both 14 and 15 had the correct relative stereochemistry at the C-3 and C-1' centers, significant amounts of the corresponding regioisomeric pair was also formed. To complete the model study, Diels-Alder adducts 14 and 15 were subjected to β-elimination and the acetonide rearranged to provide 16. Unfortunately, when 16 was vicinally hydroxylated, a mixture of epimeric acyloins 17 was obtained (34).



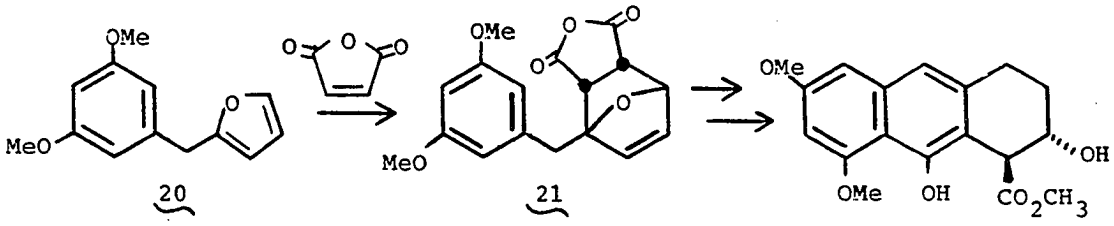
Encouraged by these results, Dalta, Franck, and Noire synthesized naphthocyclobutene 18 via a multistep route (35). Regrettably, 18 could only be induced to react with N-phenylmaleimide under forcing conditions and in low yield to provide 19.



R = $CH_2CH_2SiMe_3$

These results did not auger well for a total synthesis of olivin, in that substantially less reactive dienophiles would later be required and this strategy was not pursued further.

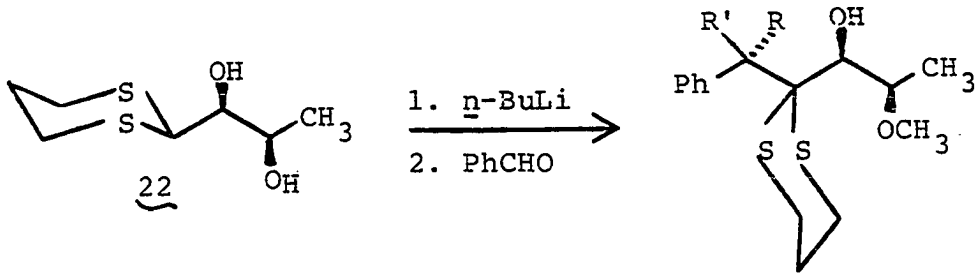
In 1983, Kraus and Hagen reported a synthetic approach to olivin and the anthracyclinone rhodomycinone (36). Reaction of furan 20 with maleic anhydride provided the Diels-Alder adduct 21. Elaboration of 21 to the olivin ring system was readily achieved employing Friedel-Crafts methodology.



20 21

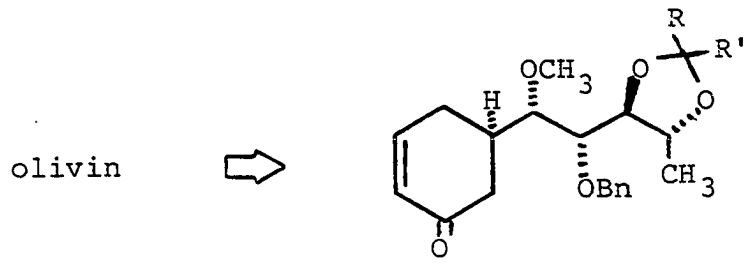
Synthetic efforts toward a model A ring and side chain were reported in 1980 by Thiem and Wessel (37). The dianion of D-threose-trimethylenedithioacetal 22, which was efficiently prepared from D-galactose, reacted with benzaldehyde to produce the epimeric alcohols 23 and 24. Although a mixture of addition products was obtained, this approach appears feasible provided that good stereoselection can be achieved with a suitably functionalized aldehyde.

An approach to a synthon for the aglycone of olivin was reported by Roush and coworkers in 1983 (38). Enone 25 was



23 R = OH, R' = H
24 R = H, R' = OH

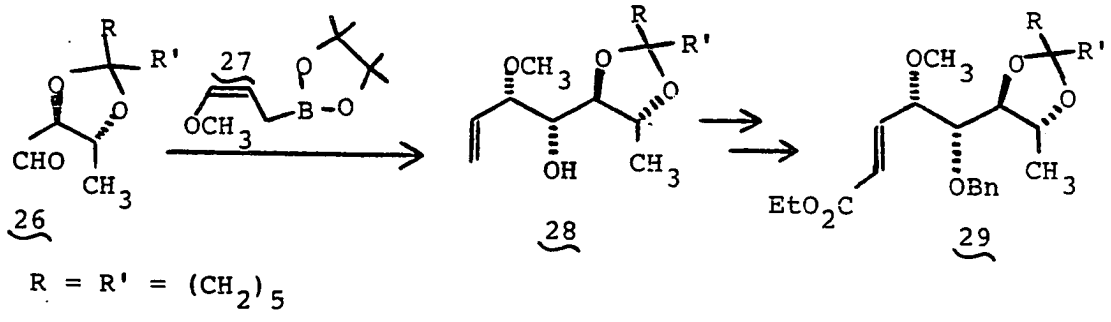
viewed as an excellent progenitor to the AB ring system and side chain of olivin.



25 R = R' = $(CH_2)_5$

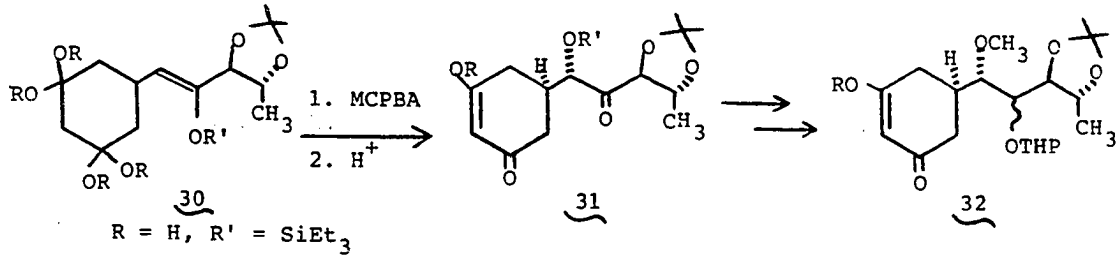
To that end, the readily available aldehyde 26 was reacted with the (Z)-boronate 27 to provide 28 with high diastereoselectivity. Elaboration of alcohol 28 to 29 was routine. To date, however, no reference to the preparation of 25 and thence to olivin has appeared.

In 1984, the first total synthesis of tri-O-methylolivin was reported by Weinreb and coworkers (39). Drawing upon results obtained from earlier model system studies, enol silyl



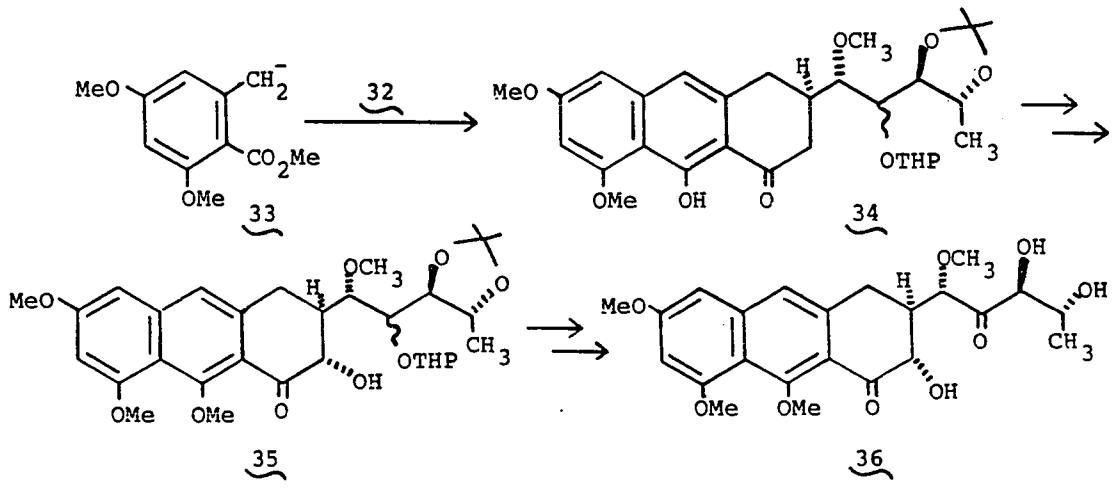
R = R' = $(CH_2)_5$

ether 30 was epoxidized and hydrolyzed with concomitant epoxide rearrangement to provide 31 as a 1:1 mixture of ring epimers. After manipulation of the functionality present in 31, a properly elaborated β-methoxystyrene synthon 32 was obtained.



R = H, R' = $SiEt_3$

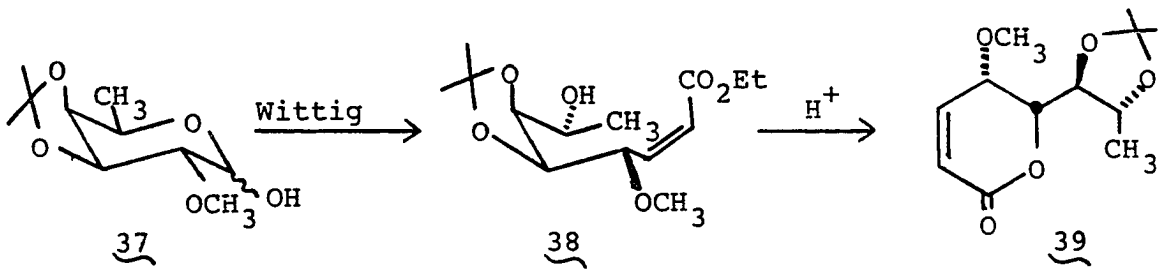
An elegant tandem Michael addition-Claisen condensation reaction of 32 with orsellinate anion 33 afforded the phenolic ketone 34 in good overall yield. Ketone 34 was then transformed in three steps to afford exclusively the trans-acyloin 35.



In a five step sequence involving protection of the acyloin, deprotection of the tetrahydropyranyl group, oxidation, and deprotections, the synthesis of tri-O-methylolivin 36 was complete. Weinreb's work provides an excellent example of CBA-ring system regiocontrol. Although adequate control at the C-2, C-3, and C-1' stereocenters was achieved, the numerous protection and deprotection steps severely diminished the efficiency of the synthesis. A highly stereocontrolled synthesis of tri-O-methylolivin was later reported by Franck and coworkers (40).

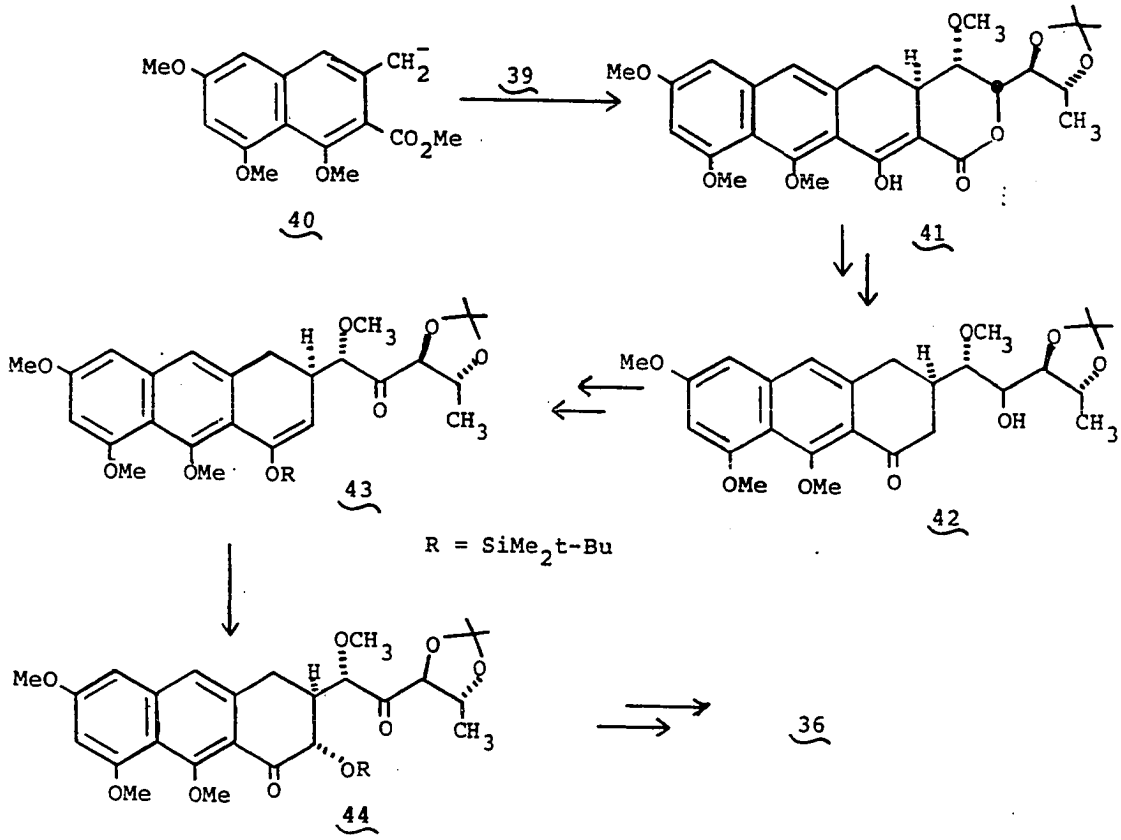
The correct absolute configuration of the side chain was established beginning with the D-fucose derivative 37. Wittig reaction with carboethoxy triphenylphosphorane produced predominantly the Z olefin 38. Rearrangement of the acetonide unit to the more stable threo glycol and lactonization

produced 39, Franck's synthon for the A-ring and side chain of olivin.



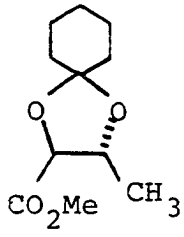
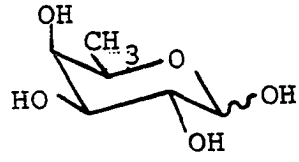
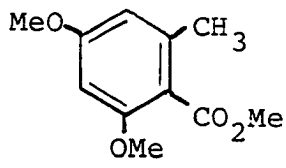
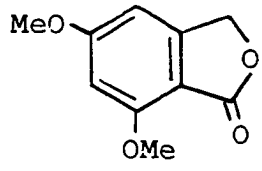
The fortuitous obtention of 38 in the Wittig reaction of 37 opened a highly efficient pathway to tri-O-methylolivin (41). In a condensation analogous to that seen in Weinreb's synthesis, naphthoate anion 40 produced 41 on reaction with lactone 39. After basic hydrolysis and decarboxylation, ketone 42 was obtained in 51% overall yield.

In the key Michael addition-Claisen condensation, conjugate addition from the face opposite the allylic methoxyl group in 39 led to complete stereochemical control at C-3. After Swern oxidation and chemoselective enol silyl ether formation, 43 was oxidized and rearranged *in situ* to produce an 8:1 mixture of acyloins 44 with the *trans*-isomer predominating. Hydrolysis of the silyl ether and acetonide protecting groups was then achieved in one step to provide tri-O-methylolivin 36.



In comparison of the two successful syntheses of tri-O-methylolivin, some important points are brought to the fore. First, regiocontrol in construction of the CBA ring system is paramount. Stereocontrol in the A-ring and side chain, particularly at C-2 and C-3, is absolutely essential to the outcome of any synthesis of olivin. Finally, a synthetic plan toward olivin should be generalizable to that of chromomycinone. A tabular analysis of the Weinreb and Franck syntheses is provided in Table 2.

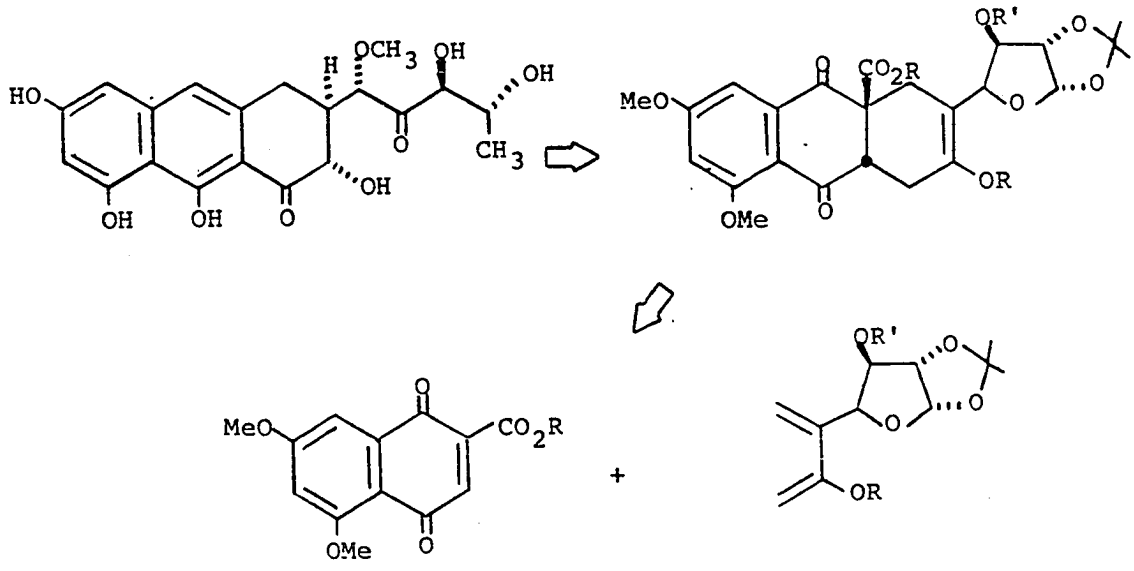
Table 2. A comparison of the Weinreb and Franck syntheses of tri-O-methyl olivin

Criterion	Weinreb's synthesis	Franck's synthesis
ratio of C-C bond forming steps to total steps required	0.11	0.20
total steps	19	15
overall yield (%)	0.61	5.65
starting material for side chain/A ring preparation		
starting material for BC ring system		

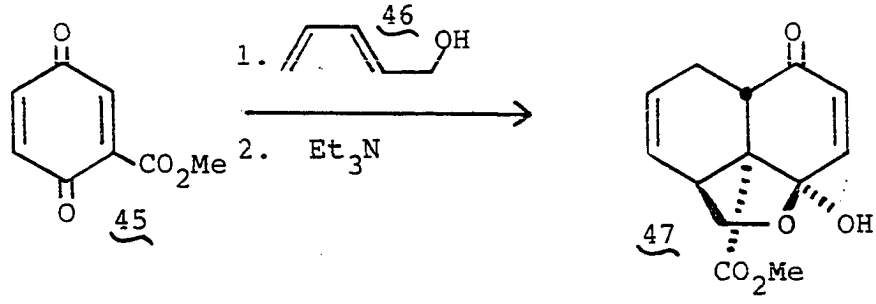
RESULTS AND DISCUSSION

Since their initial isolation in 1953, the aureolic acid group has evolved into an important class of antitumor antibiotics. Their high cytostatic activity, coupled with their unique assemblage of functionality, has prompted considerable attention from synthetic chemists. Both the tandem Michael addition-Claisen condensation and the Diels-Alder reaction have been used in synthetic approaches to the aglycones of this class of antibiotics. However, only the anionic approach has consistently been successful.

Our approach to olivin was initiated prior to the reported syntheses of tri-O-methylolivin. We envisioned a Diels-Alder based CB + A → CBA ring construction of olivin wherein the A unit would also contain latent functionality for the side chain. The Diels-Alder reaction of a highly activated 2-substituted naphthoquinone in concert with a polarized, carbohydrate diene was anticipated to occur with high regioselectivity. Removal of the activating functionality and adjacent carbonyl would then provide the olivin skeleton. Manipulation of the carbohydrate synthon and stereocontrolled C-5 methyl group introduction appeared to be a viable route to the aglycone (Scheme I).

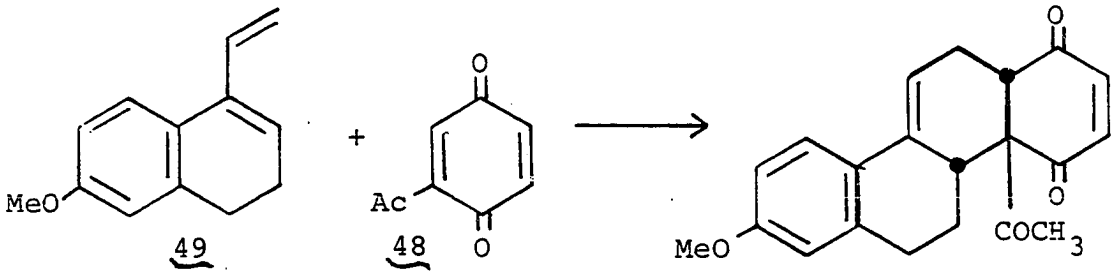


Literature precedent pertaining to the regioselectivity of the proposed Diels-Alder reaction was found in the work of Goldsmith et al. (42). In their studies toward the synthesis of ajugarin I, the Diels-Alder reaction of carbomethoxy-p-benzoquinone 45 and 2,4-pentadien-1-ol 46 was studied. Only 47 resulting from an "ortho" Diels-Alder transition state orientation was formed.

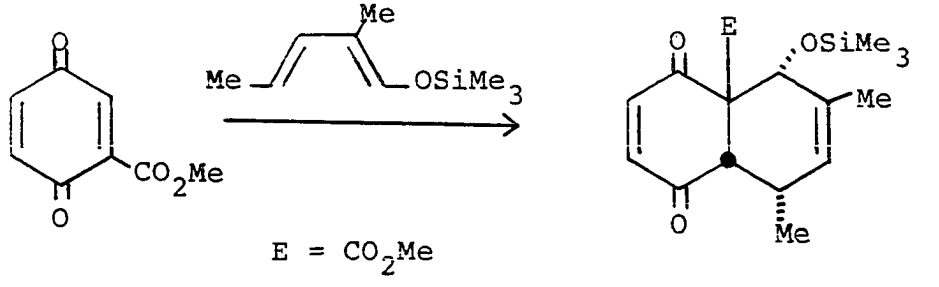


Specific additions of 1-aryl-substituted butadienes to 45 have also been studied (43). Das and coworkers have studied

the cycloaddition of 2-acetyl-p-benzoquinone 48 with the styrene derivative 49 (44). Results paralleling those of Goldsmith were obtained.

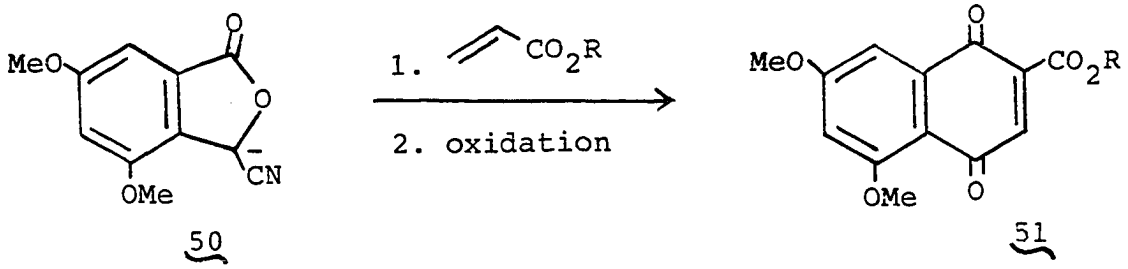


Finally, previous results from these laboratories indicated that Diels-Alder reactions between highly activated benzoquinones and butadienes with opposing directional substituents occur with a high degree of regioselectivity (45).



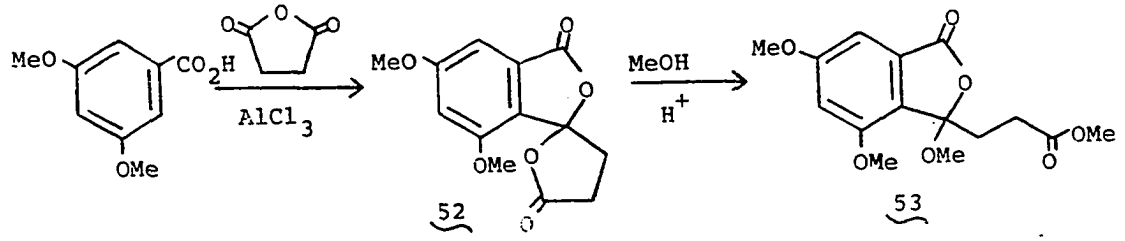
With ample literature precedent for a regioselective Diels-Alder cycloaddition, we set out to test this new approach to olivin. Requisite for our studies was the

availability of naphthoquinone esters such as 51. Previous results from our laboratory (46) indicated that the



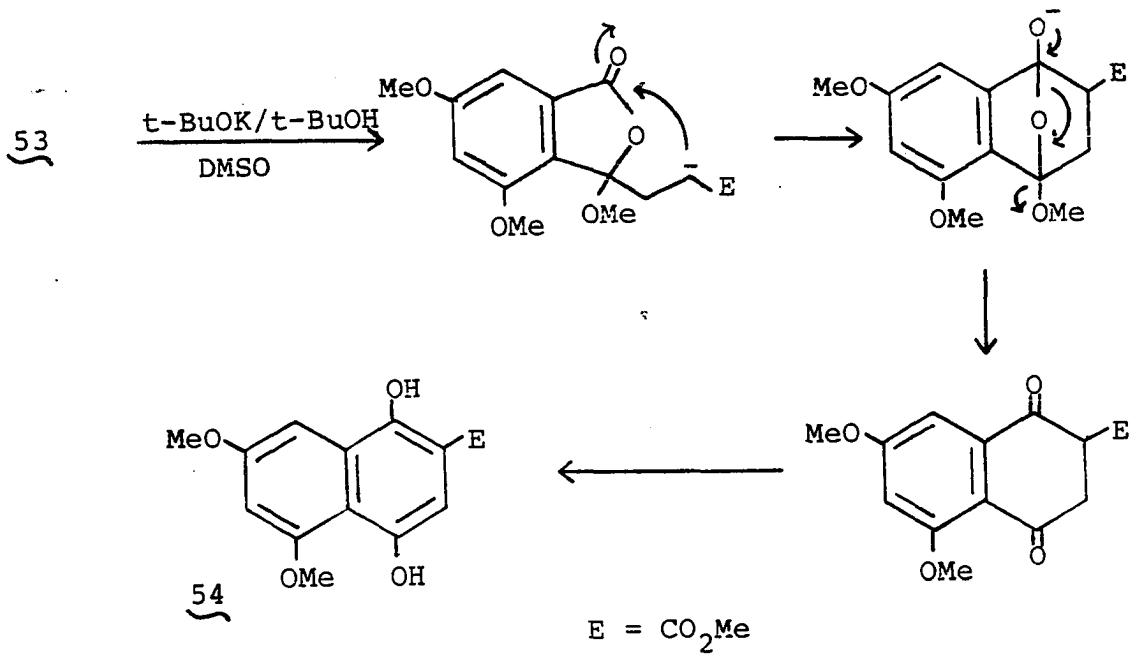
50 51

cyanophthalide annulation procedure would be applicable for the preparation of 51. However, the anticipated difficulty in preparing the needed cyanophthalide 50 led us to an alternative method (vide infra).



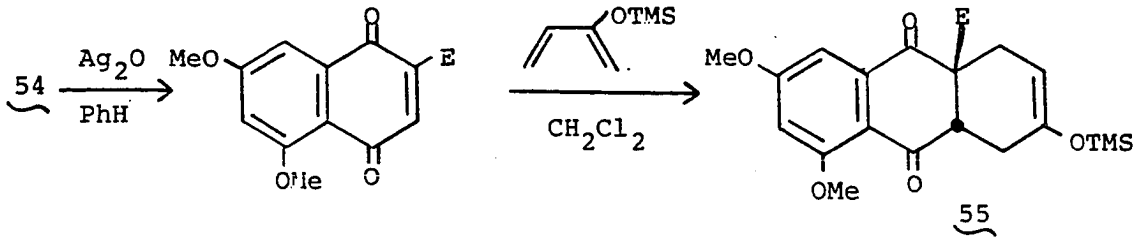
52 53

Friedel-Crafts acylation of α-resorcyclic acid dimethyl ether with succinic anhydride afforded the known spirobislactone 52 in good yield on a 20 g scale (47a). Treatment of 52 with acidic methanol produced the known sparingly soluble pseudoester 53 (47b). Dieckmann condensation (48) of 53 and *in situ* deprotonation afforded 54 in 57% yield.



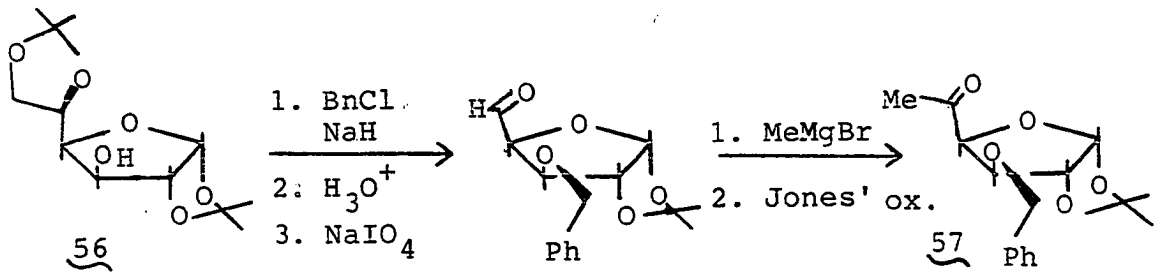
Although the generality of the above three step procedure remains to be determined, any benzoic acid derivative acylating specifically at the ortho-position relative to the carboxyl function should provide similar results.

A preliminary test for Diels-Alder regioselectivity was then undertaken. Oxidation of 54 with silver(I) oxide and immediate reaction of the unpurified quinone with 2-trimethylsilyloxybutadiene at ambient temperature produced the adduct 55 in high yield. That 55 was indeed one regioisomer was evident from its ^{13}C NMR spectrum. Proof that 55 was the desired "para" regioisomer stemmed from selective proton decoupling studies. The olefinic enol ether proton of 55 appeared as a broad triplet (J = 5 Hz) at 4.81 ppm in the

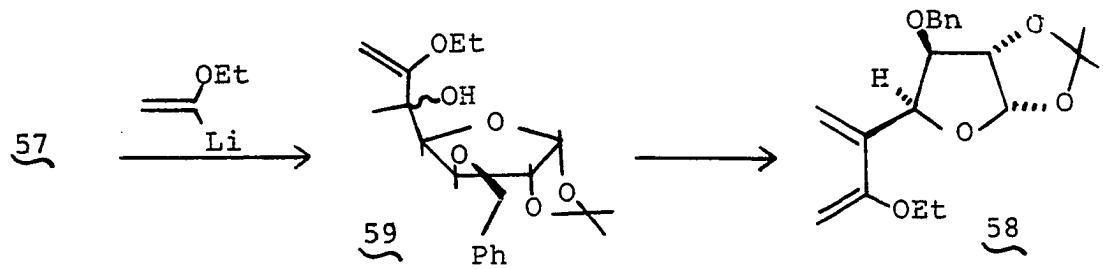


nondecoupled spectrum. When the C-5 methylene protons (anthraquinone numbering) were irradiated, the triplet at 4.81 ppm collapsed to a singlet. Irradiation of the C-8 protons had no effect on the multiplicity of the signal at 4.81 ppm. Since four bond allylic coupling constants are typically two Hertz or less (49), the above experiments demonstrate that "para" regiospecificity had been obtained.

We next turned our attention to the preparation of a suitable diene synthon for the A ring and side chain of olivin. The commercially available diacetone-α-D-glucose 56 was chosen for this purpose. By a modification of the Heathcock procedure (50), the known methyl ketone 57 (51) was prepared in five steps and in 40-50% overall yield without purification of intermediates.



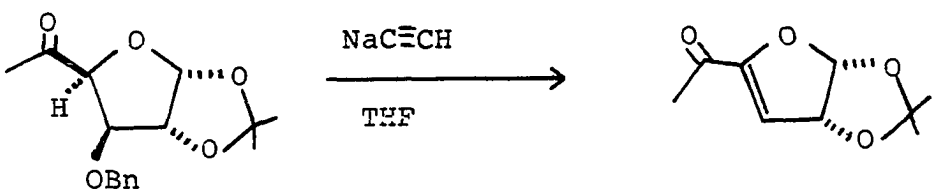
To complete the preparation of the carbohydrate diene, we envisioned addition of 1-ethoxyvinyllithium to 57 followed by dehydration to 58.



In the event, addition of an excess of 1-ethoxyvinyllithium (52) to 57 resulted in a rapid reaction, and upon workup produced an approximately 1:1 mixture of inseparable epimeric alcohols 59. Unfortunately, when the mixture of alcohols was submitted to mild acidic treatment, only highly polar unidentifiable products were obtained. Since the acidic conditions may promote carbocationic rearrangements (53), derivatization of 59 followed by E_2 type eliminations were next explored. However, only intractable tars were obtained under the following conditions: phosphorous oxychloride/pyridine (54), thionyl chloride/pyridine (55), trifluoromethanesulfonyl chloride/sodium hydride (56), and acetic anhydride/4-dimethylaminopyridine.

Another tactical approach to the desired carbohydrate substituted butadiene was then examined. It was hoped that

acetylide anion addition, followed by hydrolysis of the resulting carbinol, would produce an α-hydroxy methyl ketone. If the α-hydroxymethyl ketone could be produced, elaboration to the diene 58 might naturally follow. Surprisingly, treatment of methyl ketone 57 with sodium acetylide resulted in a facile β-elimination to provide 60, a known compound (57). Clearly the acetylide anion was not a strong enough

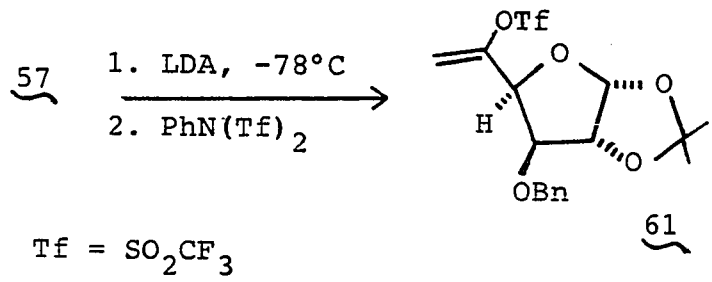


57 60

nucleophile, and deprotonation with subsequent β-elimination ensued.

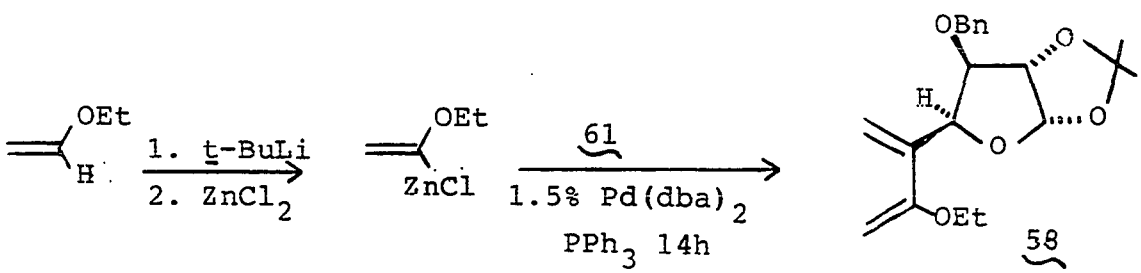
In light of these results, a strategy not involving prior carbonyl addition was indicated. A recent report by Scott, Crisp, and Stille had described palladium(0) catalyzed cross couplings of a variety of vinyl, alkyl, and acetylenic stannanes with vinyl triflates (58). While the methyl ketone 57 was relatively hindered toward nucleophilic addition, examples of cross couplings of very hindered enol triflates had been accomplished by Stille. The regiospecific formation of vinyl triflates from a variety of enolates prompted us to investigate this mode of diene preparation (59).

Deprotonation of 57 under strict kinetic enolate forming conditions followed by addition of N-phenyltrifluoromethanesulfonimide provided vinyl triflate 61 in 77% yield.



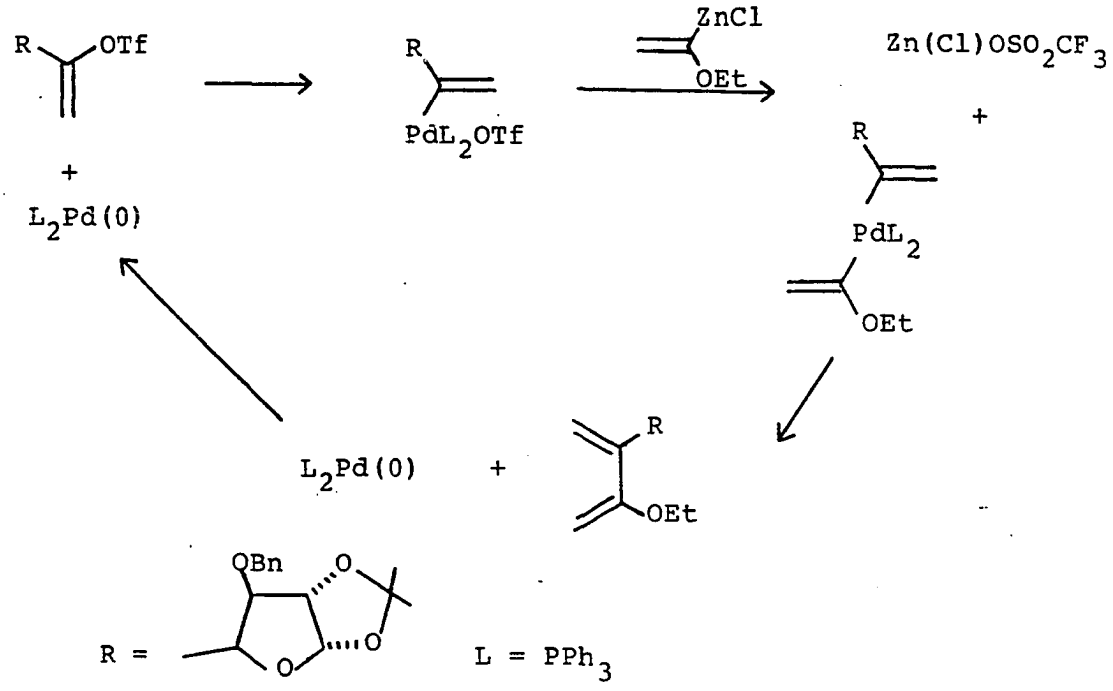
Tf = SO_2CF_3

Treatment of 61 with 1-ethoxyvinyltri-n-butylstannane under the general conditions set forth by Stille [LiCl, 2% $Pd(PPh_3)_4$] did not afford any of the desired butadiene. However, use of the corresponding vinyl zinc reagent (60) and employment of a different palladium(0) catalyst led to the formation of the desired butadiene 58 in 62% yield. To my knowledge, this is the first example of a cross coupling involving vinyl triflates and organozinc reagents (61).



A possible mechanism for this new cross coupling is detailed below in Scheme II.

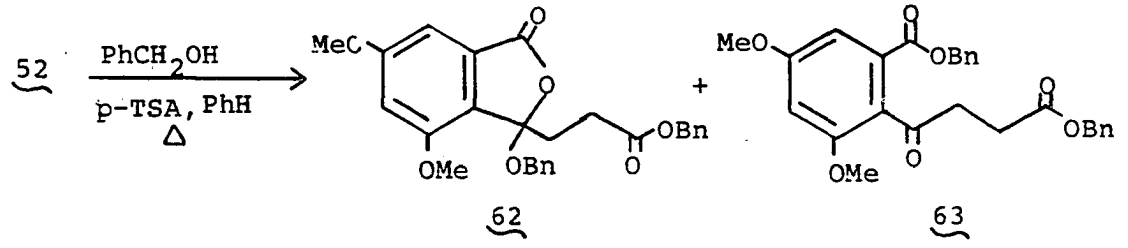
Scheme II



Displacement of the triflate in the initially formed vinylpalladium(II) intermediate by the vinylzinc followed by reductive elimination generates the diene product and regenerates the palladium(0) catalyst (62). The failure of the Stille cross coupling may be due in part to the steric hindrance to attack of the organostannane (transmetallation) on the initially formed palladium(II) intermediate. The vinylzinc reagent is clearly more nucleophilic than the vinylstannane and this enhanced reactivity may account for the

success of the organozinc modification. Similar cross couplings of in situ generated alkylzinc reagents and vinyl bromides have been reported by Negishi and coworkers (63).

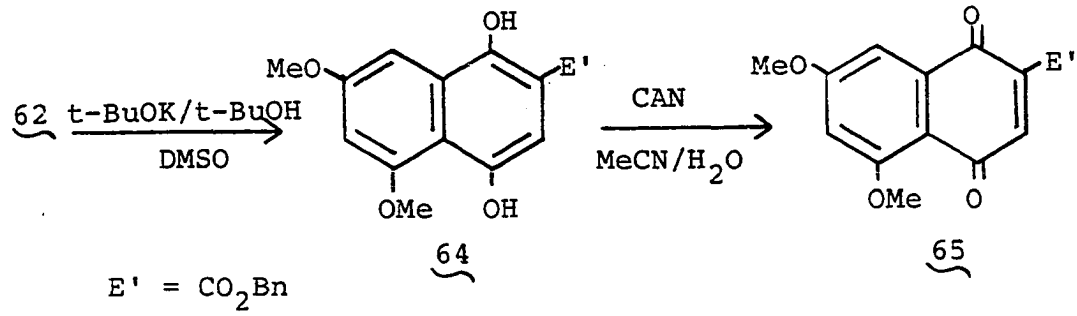
With the complex carbohydrate substituted diene in hand, we focused our attention on the crucial Diels-Alder reaction that would join the CB and A ring components. Due to the poor solubility properties of pseudo-ester 53 (vide supra), the corresponding benzyl pseudo-ester was prepared. Treatment of spirobislactone 52 with excess benzyl alcohol in refluxing benzene containing a catalytic amount of p-toluene-sulfonic acid resulted in the formation of the desired 62 in 80% yield accompanied by small amounts of ketodiester 63. By using



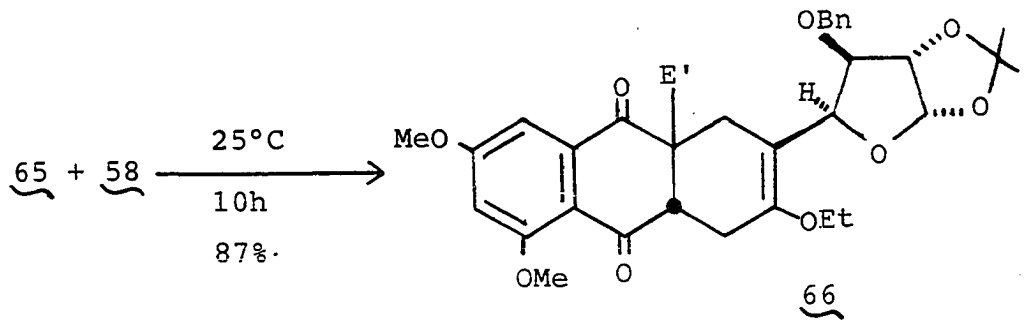
62 63

prolonged reaction times, the amount of 63 produced was held to a minimum.

Dieckmann condensation produced 64 in 66% yield. Oxidation of 64 with ceric ammonium nitrate (64) in aqueous acetonitrile produced naphthoquinone 65 in 97% yield. Diels-Alder cycloaddition of 65 and 58 was complete after 10 hours of stirring in benzene at ambient temperature. The

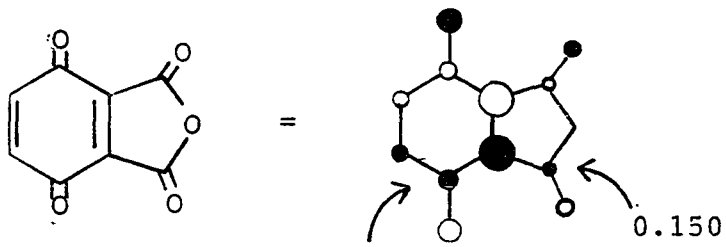


clean methylene signals in the ^{1}H NMR spectrum for a benzyl ester and ether at 5.04 ppm and 4.48 ppm respectively (both AB quartets), attested to the presence of only one diastereomer. The product was formulated on the basis of secondary orbital interactions and steric considerations as 66 (vide infra).



Although the stereochemistry at the ring juncture formed in the cycloaddition reaction relative to that of the carbohydrate residue is of no consequence to the overall outcome of this approach, an analysis of the factors responsible for the production of only one diastereomer seems appropriate. In Diels-Alder cycloadditions of quinones with electron withdrawing substituents and dienes bearing

substituents in the 2- and 3-positions, two considerations are important in predicting the major product(s) (65). First, the relative importance of quinone carbonyls versus the electron attracting substituent in controlling secondary orbital interactions must be considered (66). Molecular orbital calculations using the MNDO MO method of Kanematsu and coworkers clearly indicate that the LUMO coefficients at C-1 and C-4 of 67 are much larger than those of C-7 and C-8 (67).



67

By analogy, the quinone carbonyls of 65 would be expected to have larger LUMO coefficients than the carbonyl of the benzyl ester, and thus control secondary orbital interactions in the Diels-Alder transition state.

In light of the previous discussion, only two endo transition states need to be considered for the product analysis; endo-syn, wherein the ethereal benzyl group projects toward the naphthoquinone, and endo-anti, with the benzyl group projecting away from the quinone. The two transition

states and the resulting products that would be formed are shown in figure 2.

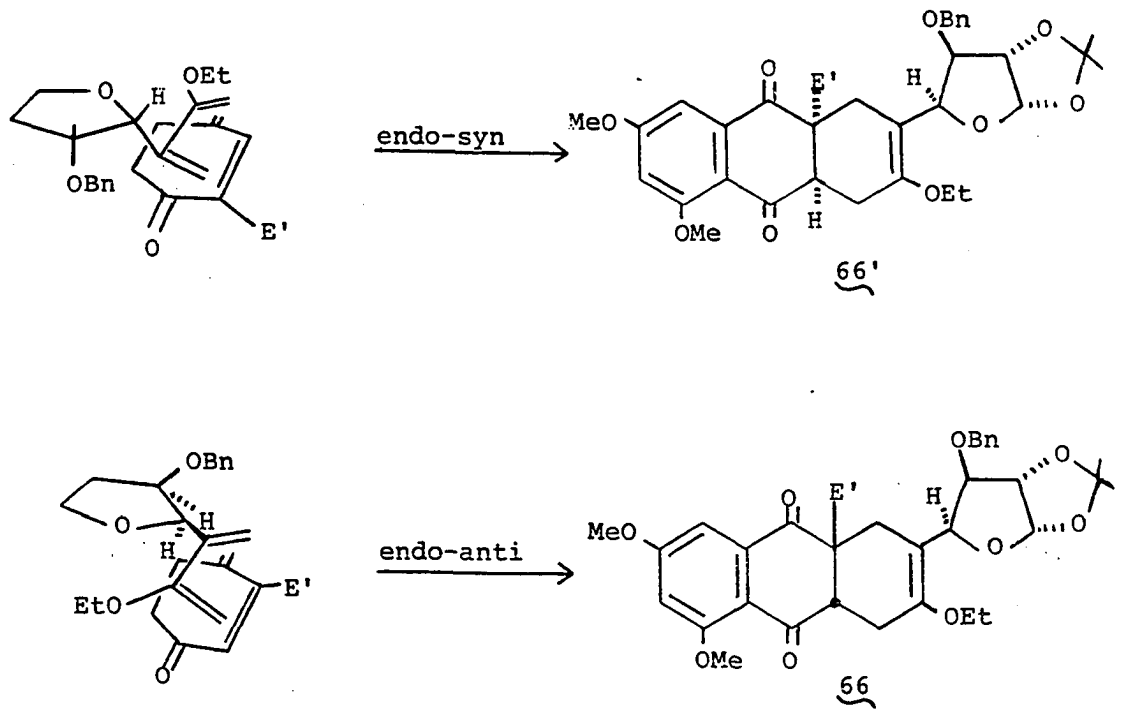
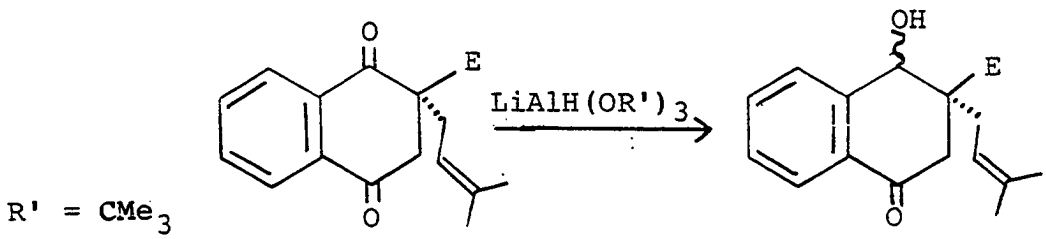


Figure 2. Endo transition states for the cycloaddition reaction of 65 and 58

In the endo-syn transition state, severe steric repulsion of the benzyl ether group and one carbonyl of the quinone is evident. In the endo-anti transition state, these interactions are absent. Thus, the probable structure of the Diels-Alder adduct of 65 and 58 is 66.

The obtention of Diels-Alder adduct 66 demonstrates our strategy for the synthesis of the olivin aglycone is feasible. Although efforts to synthesize olivin from 66 were temporarily halted at this point, the following partial proposed synthesis from 66 should prove practicable (Scheme III). Reduction of 66 at the most electrophilic carbonyl employing the conditions of Inoue et al. (68) should yield 68 selectively. In their studies, a similar selectivity was achieved due to the inductive electron withdrawal of an adjacent carbomethoxyl group.

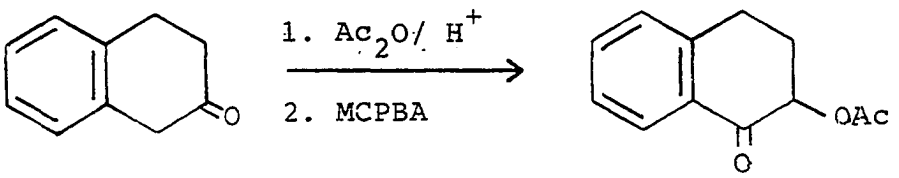


R' = CMe_3

In addition to this same interaction in 66, the electron donating effect of the C-1 and C-3 methoxyl groups should enhance the selectivity.

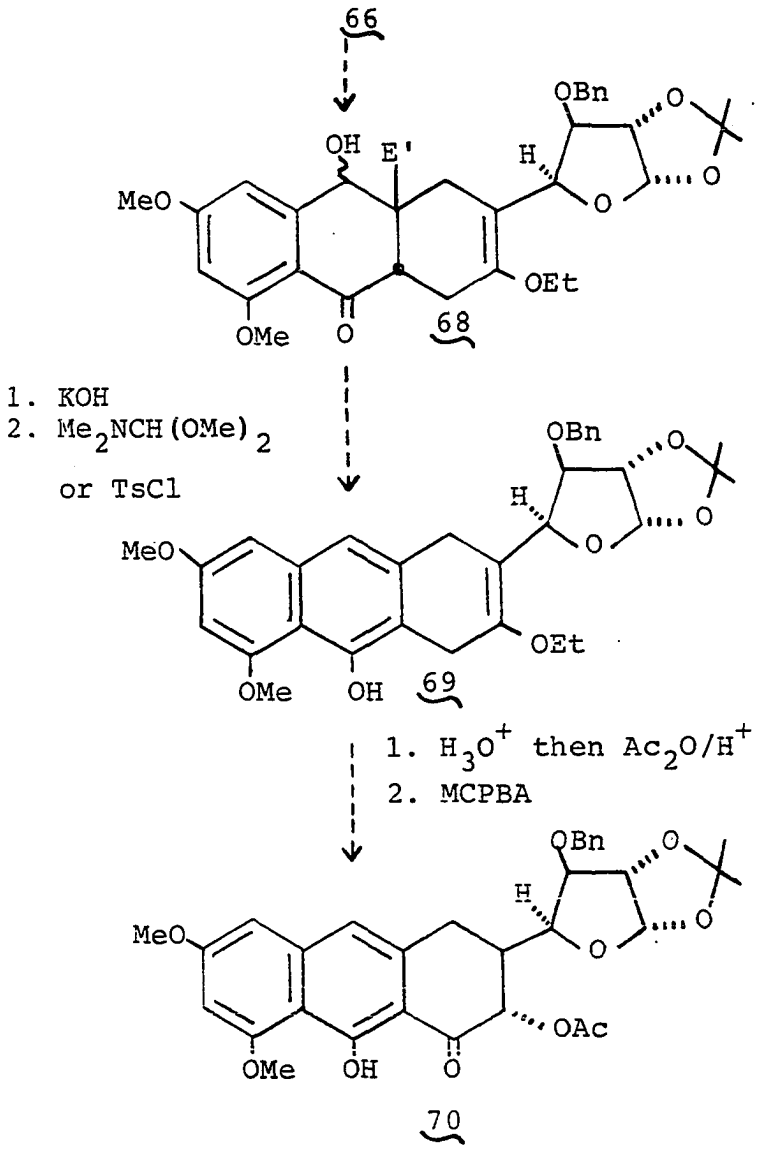
Saponification of 68 followed by treatment of the acid with the dimethylacetal of dimethylformamide and mild heating should produce 69 after aromatization of the B ring (69). Should this reaction prove troublesome, a three step procedure involving saponification, tosylation, and decarboxylative

β-elimination should be workable. Once 69 is in hand, hydrolysis of the labile enol ether, reenolization to the conjugated enol acetate, and oxidation should provide the trans acyloin 70 (70). The latter two steps have already been accomplished in a related model system by a coworker in these laboratories (71). Compound 70 has all of the necessary



functionality intact for eventual conversion to tri-O-methyl-olivin or a similar olivin derivative.

Scheme III


66
OBn
OH
E'
H
MeO
OEt
OMe
O
68
1. KOH
2. $Me_2NCH(OMe)_2$
or TsCl
69
1. H_3O^+ then Ac_2O/H^+
2. MCPBA
OAc
70

EXPERIMENTAL

General

Unless otherwise noted, materials were obtained from commercial suppliers and were used without purification. THF and diethyl ether were distilled from sodium benzophenone ketyl under nitrogen prior to usage. Benzene was distilled from lithium aluminum hydride. Dichloromethane was distilled from calcium hydride. Unless otherwise noted, all reactions were conducted under an argon atmosphere. Unless otherwise noted, all organic extracts were dried over anhydrous sodium sulfate. Melting points were determined on a Fisher-Johns melting point apparatus and are uncorrected. Infrared spectra were obtained on a Beckman IR-4250 or a Perkin-Elmer model 1320 spectrophotometer. Nuclear magnetic resonance spectra were determined on a Varian EM-360 spectrometer. High field (300 MHz) proton spectra were obtained with a Nicolet Magnetics Corporation NMC-1280 spectrometer. All chemical shifts are reported in δ relative to tetramethylsilane as an internal standard. Coupling constants (J) are reported in Hz. Abbreviations: s = singlet, d = doublet, t = triplet, q = quartet, bs = broad singlet, m = multiplet, ABq, AB quartet. Carbon-13 NMR spectra were determined on a Nicolet NMC-1280 spectrometer and are reported in ppm relative to the central peak of $CDCl_3$ (77.06 ppm). High-resolution mass spectra were recorded on a Kratos model MS-50 spectrometer. Low-resolution

mass spectra were recorded on a Finnegan 4023 mass spectrometer. Silica gel used for flash chromatography (72) was 230-400 mesh (Kieselgel 60) purchased from EM Science. Gravity column chromatography was performed on 60-200 mesh silica gel purchased from Davison Chemical (WR Grace Inc.). Elemental analyses were performed by Galbraith Laboratories, Inc.

1,4-Dihydroxy-5,7-dimethoxy-2-naphthoic Acid, Methyl Ester (54)

To a solution of pseudo-ester 53 (402 mg, 1.29 mmole) in 20 mL of dry dimethylsulfoxide at 20°C was added potassium tert-butoxide/tert-butyl alcohol complex (770 mg, 4.15 mmole) in 10 mL dimethylsulfoxide. The resulting red solution was stirred at ambient temperature for 4 h, then acidified with 1.5 N HCl until the red color was discharged. The resulting yellow solution was poured into 50 mL water, and extracted with ether. The combined extracts were washed with brine and dried. Chromatography on silica gel using 3:1 hexanes/ethyl acetate as solvent afforded 207 mg (57%) of 54: mp 166-168°C; 300 MHz ^{1}H NMR ($CDCl_3$) δ 3.93 (s, 3 H), 3.97 (s, 3 H), 4.02 (s, 3 H), 6.6 (d, 1 H, J = 2.1 Hz), 7.00 (s, 1 H), 7.29 (d, 1 H, J = 2.1 Hz), 8.62 (s, 1 H), 11.33 (s, 1 H); IR ($CDCl_3$) 3680, 3420, 3040, 2980, 1665, 1618, 1588, 1435, 1210, 1165, 1140, 1040, 1010, 890 cm^{-1}; MS, m/e 278, 246, 218, 190, 123;

high-resolution mass spectrum for $C_{14}H_{14}O_6$ requires 278.07904, measured 278.07877.

(±)-(8aβ,10aβ)-10a-Carbomethoxy-1,3-dimethoxy-7-[(trimethylsilyl)oxy]-5,8,8a,10a-tetrahydro-9,10-anthracenedione (55)

To a solution of 54 (27.1 mg, 0.097 mmole) in 5 mL of dry benzene at 5°C was added silver(I) oxide (46.3 mg, 0.20 mmole). The reaction mixture was shielded from light and stirred at ambient temperature for 75 min. The resulting yellow-orange solution was filtered through Celite and the solvent removed in vacuo to yield the naphthoquinone as a deep orange solid: 60 MHz ^{1}H NMR ($CDCl_3$) δ 4.01 (bs, 6 H), 6.80 (d, 1 H, J = 2 Hz), 7.22 (s, 1 H), 7.28 (d, 1 H, J = 2 Hz); IR ($CDCl_3$) 2930, 1735, 1647, 1588, 1230, 1140, 1075 cm^{-1}.

The naphthoquinone was used immediately without further purification. To a solution of the naphthoquinone in 2 mL of methylene chloride was added 1-(trimethylsilyloxy)-1,3-butadiene (50 μL, 0.27 mmole) at 0°C. The reaction mixture was slowly warmed to ambient temperature and stirred 6 h at ambient temperature. The solvent was removed on a rotary evaporator and the remaining volatiles removed in vacuo to yield 31.3 mg (77%) of 55 as a beige solid: beige needles recrystallized from hexane-diethyl ether, mp 171-172°C; 300 MHz ^{1}H NMR ($CDCl_3$) δ 0.21 (s, 9 H), 21.8 (m, 2 H), 2.58 (m, 2 H), 3.73 (s, 3 H), 3.80 (t, 1 H), 3.90 (s, 3 H), 3.91 (s, 3 H), 4.81 (bt, 1 H), 6.73 (d, 1 H, J = 2.4 Hz), 7.13 (d, 1 H, J

= 2.4 Hz); ^{13}C NMR 194.02, 192.37, 170.21, 164.57, 161.31, 147.89, 136.46, 116.51, 105.25, 102.67, 100.52, 59.66, 56.39, 55.77, 52.76, 49.95, 27.75, 27.45, 0.162 ppm; IR (CH_2Cl_2) 3040, 2950, 2895, 2840, 1738, 1683, 1593, 1455, 1315, 1215, 1205, 1150, 850, 648 cm^{-1}; MS, m/e 418, 403, 390, 371, 359, 344, 327, 313; high-resolution mass spectrum for $C_{21}H_{26}O_7Si$ requires 418.14479, measured 418.14509.

6-Deoxy-1,2-0-(1-methylethylidene)-3-0-(phenylmethyl)-α-D-xylo-hexofuranos-5-ulose (57)

The literature procedure (48) for the corresponding ethyl ketone was modified. To a stirred suspension of hexane washed sodium hydride (2.35 g, 97.9 mmole) in 100 mL of THF was added diacetone-D-glucose (25.0 g, 95.9 mmole) in 50 mL of THF dropwise. To the resulting suspension was added 12.5 mL of dimethylsulfoxide and the reaction mixture warmed to a gentle reflux to dissolve the suspension. After the suspension had dissolved, benzyl chloride (11.04 mL, 96.0 mmol) was added and reflux was continued for 3 h. The reaction mixture was cooled, poured into 620 mL of water, and the aqueous solution saturated with sodium chloride. The saturated sodium chloride solution was extracted three times with 100 mL portions of diethyl ether, and the ethereal layers were combined and washed with four 100 mL portions of water, dried, and the solvent removed in vacuo to yield 33.3 g (99%) of the benzyl ether which was used without purification.

The benzyl ether (33.3 g, 95.0 mmole) was dissolved in 250 mL of 60% (v/v) acetic acid and stirred at ambient temperature for 22 h. The solvents were removed *in vacuo*, and the residue was dissolved in 50 mL of toluene and evaporated *in vacuo* (repeated two times). The crude 5,6-diol was dissolved in 375 mL of absolute ethanol, treated with 40 mL of saturated sodium bicarbonate solution and 21 g of sodium metaperiodate in 750 mL of water. After 2.5 h of stirring at ambient temperature, the reaction mixture was treated with 500 mL of ethanol and the precipitated salts were filtered, and the filtrate concentrated *in vacuo*. The residue was repeatedly treated with 100 mL of ethanol, filtered, and concentrated until no further precipitation occurred on addition of ethanol. The resulting aldehyde which was contaminated with residual ethanol and water was coevaporated three times with toluene, dissolved in 75 mL of THF, and treated at 0°C with methylmagnesium bromide (54.6 mL of a commercial 2.7 M THF solution, 147.5 mmole) dropwise over 30 min. The light yellow solution was stirred 10 min at 0°C, then poured into 250 mL of saturated ammonium chloride and 100 mL of diethyl ether. The organic layer was separated and the aqueous layer was extracted twice with 50 mL portions of diethyl ether. The ethereal layers were washed with 150 mL of 1 N HCl, 150 mL of saturated sodium bicarbonate and dried to afford 23.1 g (81%) of the carbinol as a mixture of diastereomers by TLC.

To a solution of the carbinol (5.4 g, 18.1 mmole) in 150 mL of acetone at -65°C was added 8 ml of the Jones reagent, prepared by the method of Djerassi et al. (73), and slowly warmed to -5°C over 1 h. An additional 4 ml of the Jones reagent was then added and stirring continued for 2 h at 0°C. The reaction was then quenched with 3 ml of isopropanol, and filtered through 4 inches of Florisil. The solvents were removed in vacuo, and the residue was flash chromatographed on 40 g of silica gel eluting with 2.3:1 hexanes-diethyl ether to afford 2.8 g of pure 57 which crystallized on standing: mp 56-57°C (lit. (49) 55-56°C); 300 MHz ^{1}H NMR ($CDCl_3$) δ 1.33 (s, 3 H), 1.47 (s, 3 H), 2.22 (s, 3 H), 4.265 (d, 1 H, J = 3.9 Hz), 4.53 (ABq, 2 H, J_{gem} = 11.7 Hz), 4.605 (d, 1 H, J = 3.6 Hz), 4.63 (d, 1 H, J = 3.6 Hz), 6.08 (d, 1 H, J = 3.6 Hz), 7.3 (m, 5 H); ^{13}C NMR 72.34, 81.84, 83.69, 85.35, 105.82, 112.07, 127.48, 127.83, 128.28, 136.84, 206.15 ppm; IR (film) 3060, 3025, 2982, 2930, 2860, 1718, 1453, 1382, 1372, 1353, 1216, 1162, 1110, 1075, 1025, 855, 735, 695 cm^{-1}; Anal. Calcd for $C_{16}H_{20}O_5$: C, 65.75; H, 6.85. Found: C, 65.48; H, 7.08.

Attempted Addition of Sodium Acetylide to (57)

To a solution of 57 (177 mg, 0.60 mmole) in 5 mL of THF at 0°C was added sodium acetylide (1 ml of a 11-15% commercial suspension, ~ 2 mmole) dropwise. After warming the suspension to ambient temperature and stirring for 1.5 h, the reaction mixture was quenched with a pH = 7.0 phosphate buffer and

poured into water. The aqueous layer was extracted twice with two 20 mL portions of diethyl ether, and the ethereal layers were dried. The solvents were removed in vacuo to afford 93 mg (92%) of 60 as a clear oil: compound 60 is a known compound (54). 60 MHz ^{1}H NMR ($CDCl_3$) δ 1.50 (s, 6 H), 2.35 (s, 3 H), 5.4 (dd, 1 H, J = 10 Hz, 4 Hz), 6.05 (d, 1 H, J = 4 Hz), 6.20 (d, 1 H, J = 10 Hz).

5,6-Dideoxy-5-[(trifluoromethanesulfonyl)oxy]-1,2-O-(1-methylethylidene)-3-O-(phenylmethyl)-α-D-xylo-hex-5-enofuranose (61)

To a solution of diisopropylamine (0.63 mL, 4.5 mmole) in 25 mL of THF at 0°C was added n-butyllithium (1.82 mL of a 2.47 M solution in hexanes, 4.5 mmole) dropwise. After stirring 10 min at 0°C, the solution was cooled to -70°C and 57 (1.06 g, 3.58 mmol) in 10 mL of THF was added dropwise never allowing the internal temperature to rise above -65°C. When the addition was complete, the reaction mixture was stirred at -70°C for 30 min. To the resulting solution was added N-phenyltrifluoromethanesulfonimide (1.53 g, 4.28 mmole) in 4 mL of THF and the reaction mixture was slowly warmed to ambient temperature over 16 h. The solvents were removed in vacuo and the residue was flash chromatographed on silica gel eluting with 5:1 hexanes-diethyl ether to provide 920 mg (77%) of 61 as a clear oil: 300 MHz ^{1}H NMR ($CDCl_3$) δ 1.32 (s, 3 H), 1.49 (s, 3 H), 4.10 (d, 1 H, J = 3.3 Hz), 4.60 (ABq, 2 H, J_{gem} = 11.7 Hz), 4.625 (d, 1 H, J = 3.6 Hz), 4.75 (m, 1 H), 5.385

(dd, 1 H, J = 3.6 Hz, 0.9 Hz), 5.465 (dd, 1 H, J = 3.6 Hz, 1.2 Hz), 5.99 (d, 1 H, J = 3.6 Hz), 7.30 (m, 5 H); ^{13}C NMR 26.40, 27.03, 72.69, 78.88, 81.46, 82.53, 105.31, 106.32, 112.62, 127.82, 128.12, 128.53, 137.01, 149.63 ppm; IR (CCl_4) 3060, 3040, 2985, 2930, 2870, 1675, 1596, 1452, 1420, 1383, 1372, 1215, 1140, 1075, 1030, 939, 790, 695 cm^{-1}; MS m/e 409, 333, 291, 260, 129, 91; high-resolution mass spectrum for $C_{16}H_{16}O_7SF_3$ requires 409.05693, measured 409.05690.

5,6-Dideoxy-5-etheneyl-6-ethoxy-1,2-O-(1-methylethylidene)-3-O-(phenylmethyl)-α-D-xylo-hept-6-enofuranose (58)

To a solution of ethyl vinyl ether (0.20 mL, 2.0 mmole) in 16 mL of THF at -78°C was added tert-butyllithium (1.17 mL of a 1.7 M solution in pentane, 2.0 mmole). The solution was slowly warmed to 0°C over 30 min whereupon the yellow color faded to a clear colorless solution. After warming to ambient temperature, zinc chloride (300 mg, 2.2 mmol) in 5 mL of THF was added. After 5 min bis(dibenzalacetone)palladium(O) (14.5 mg, 0.024 mmole) and triphenylphosphine (13 mg, 0.05 mmol) in 5 mL of THF were added followed by 61 (173 mg, 0.40 mmol) in 2 mL THF. The reaction mixture was stirred 14 h at ambient temperature, stripped down to dryness, taken up in 20 mL of diethyl ether and poured into a dilute pH = 7.0 phosphate buffer. The layers were separated and the aqueous layer was extracted with 20 mL of diethyl ether. The ethereal layers were combined, washed with brine and dried. The solvents were

removed in vacuo and the residue was flash chromatographed on silica gel eluting with 5:1 hexanes-diethyl ether to provide 86.8 mg (62%) of 58 as a pale yellow oil: 300 MHz ^{1}H NMR ($CDCl_3$) δ 1.308 (t, 3 H, J = 6.9 Hz), 1.32 (s, 3 H), 1.50 (s, 3 H), 3.74 (dq, 2 H, J = 6.9), 4.025 (d, 1 H, J = 2.7 Hz), 4.045 (d, 1 H, J = 3.0 Hz), 4.25 (d, 1 H, J = 2.7 Hz), 4.48 (bs, 2 H), 4.60 (d, 1 H, J = 3.9 Hz), 4.95 (bs, 1 H), 5.56 (bs, 1 H), 5.78 (bs, 1 H), 5.99 (d, 1 H, J = 3.6 Hz), 7.27 (m, 5 H); ^{13}C NMR 14.33, 26.34, 26.86, 62.83, 72.37, 79.13, 82.21, 82.53, 83.49, 104.17, 111.43, 114.63, 127.54, 127.69, 128.16, 137.60, 137.92, 158.06 ppm; IR (CCl_4) 3060, 3025, 2985, 2930, 2860, 1650, 1490, 1455, 1415, 1210, 1160, 1072, 695 cm^{-1}; MS m/e 347, 346, 255, 229, 178, 149, 129, 105; high-resolution mass spectrum for $C_{20}H_{26}O_5$ requires 346.17803, measured 346.17812. Compound 58 is unstable at room temperature and was used immediately after purification.

3-(3-Benzylpropanoatyl)-3-benzyloxy-4,6-dimethoxy-1(3 H)-isobenzofuranone (62)

To a suspension of impure 52 (15.0 g, ~ 45 mmole) in 250 mL of benzene was added benzyl alcohol (45 ml, 435 mmole) and p-toluenesulfonic acid monohydrate (2 g, 10.5 mmole) and the mixture heated at reflux for 5 d, cooled and poured with vigorous stirring into 1.2 L of cold water. The resulting gummy orange solid was filtered, dried in vacuo, and chromatographed on 600 g of silica gel eluting with 1:1

hexanes-diethyl ether to afford 13.86 g (66%) of 62 as a clear pale yellow oil: 300 MHz ^{1}H NMR ($CDCl_3$) δ 2.43 (m, 2 H), 2.73 (m, 2 H), 3.81 (s, 3 H), 3.86 (s, 3 H), 4.20 (ABq, 2 H, J_{gem} = 11.1 Hz), 5.03 (s, 2 H), 6.69 (d, 1 H, J = 1.8 Hz), 6.92 (d, 1 H, J = 1.8 Hz), 7.31 (m, 10 H); ^{13}C NMR 28.56, 32.91, 55.65, 55.84, 66.04, 66.16, 96.03, 99.11. 104.98, 109.22, 125.91, 127.53, 127.61, 127.95, 128.01, 128.33, 130.72, 135.88, 136.90, 155.65, 163.88, 167.39, 172.28 ppm; IR (film) 3060, 3025, 2930, 2830, 1760, 1730, 1618, 1490, 1447, 1422, 1318, 1140, 1040, 1020, 896, 720, 685 cm^{-1}; MS m/e 462, 356, 299, 265, 248, 219, 165, 91; Anal. Calcd for $C_{27}H_{26}O_7$: C, 70.10; H, 5.63. Found: C, 70.12; H, 5.77. Characterization for 2-(4-benzyl-4-oxo-butanoatyl)-3,5-dimethoxy-benzoic acid, benzyl ester (63), clear oil: 300 MHz ^{1}H NMR ($CDCl_3$) δ 2.63 (t, 2 H, J = 7.8 Hz), 3.08 (t, 2 H, J = 7.8 Hz), 3.76 (s, 3 H), 3.83 (s, 3 H), 5.12 (s, 2 H), 5.25 (s, 2 H), 6.61 (d, 1 H, J = 2.4 Hz), 7.05 (d, 1 H, J = 2.4 Hz), 7.35 (m, 10 H); ^{13}C NMR 28.50, 39.30, 55.77, 56.17, 66.27, 67.62, 103.08, 106.18, 126.24, 128.12, 128.47, 128.54, 128.59, 128.66, 129.97, 135.39, 136.30, 157.49, 161.11, 165.78, 172.70, 202.70 ppm; IR (film) 3040, 2965, 2845, 1730, 1715, 1605, 1455, 1325, 1240, 1210, 1145, 1058, 840, 780, 725, 692 cm^{-1}; MS m/e 462, 299, 265, 219, 165, 91; high-resolution mass spectrum for $C_{27}H_{26}O_7$ requires 462.16786, determined 462.16830.

1,4-Dihydroxy-5,7-dimethoxy-2-naphthoic Acid, Benzyl Ester (64)

To a solution of potassium tert-butoxide/tert-butanol complex (650 mg, 3.5 mmole) in 8 mL of dimethylsulfoxide at ambient temperature was added 62 (506 mg, 1.09 mmole) in 2 mL of dimethylformamide with stirring. After stirring at ambient temperature for 75 min the red solution was quenched with 1.5 N HCl until the red color was discharged. The resulting yellow solution was poured into 50 mL of water and extracted three times with 25 mL portions of diethyl ether. The extracts were combined, washed with brine, and dried. Flash chromatography on silica gel with 4:1 hexanes-ethyl acetate as eluant provided 303 mg (79%) of 64. A small sample was crystallized from ethyl acetate: mp softens 145°C, melts 174.5-176°C; 300 MHz ^{1}H NMR ($CDCl_3$) δ 3.94 (s, 3 H), 4.02 (s, 3 H), 5.40 (s, 2 H), 6.63 (d, 1 H, J = 2.1 Hz), 7.06 (s, 1 H), 7.31 (d, 1 H, J = 2.1 Hz), 7.38 (m, 5 H), 8.63 (s, 1 H), 11.33 (s, 1 H); ^{13}C NMR 55.54, 56.32, 66.99, 95.95, 101.25, 104.46, 106.98, 114.75, 127.80, 128.18, 128.41, 128.66, 135.48, 146.14, 152.31, 156.81, 157.97, 170.56 ppm; IR ($CDCl_3$) 3420, 3200-2800, 2965, 1660, 1618, 1585, 1448, 1390, 1208, 1165, 1140, 1040, 790, 690 cm^{-1}; MS m/e 355, 354, 265, 263, 219, 91; Anal. Calcd for $C_{20}H_{18}O_6$: C, 67.77; H, 5.09. Found: C, 67.62; H, 5.37.

2-Carbobenzyloxy-5,7-dimethoxy-1,4-naphthalenedione (65)

To a solution of 64 (175 mg, 0.49 mmole) in 20 mL of acetonitrile and 5 mL of THF at ambient temperature was added with stirring a solution of ceric ammonium nitrate (600 mg, 1.08 mmole) in 2 mL of water. The resulting yellow-orange solution was stirred at ambient temperature for 30 min and then poured into water. The aqueous layer was extracted twice with 30 mL portions of chloroform, the organic extracts combined, washed with water, and dried over magnesium sulfate. The solvents were removed in vacuo to provide 168 mg (97%) of 65 as a yellow-orange solid. A small sample was recrystallized from carbon tetrachloride-methylene chloride: mp 147-148°C; 300 MHz ^{1}H NMR ($CDCl_3$) δ 3.93 (s, 3 H), 3.95 (s, 3 H), 5.34 (s, 2 H), 6.73 (d, 1 H, J = 2.4 Hz), 7.16 (s, 1 H), 7.24 (d, 1 H, J = 2.4 Hz), 7.38 (m, 5 H); ^{13}C NMR 56.07, 56.55, 67.78, 104,08, 104.51, 114.59, 128.37, 128.59, 128.74, 135.16, 136.07, 136.88, 141.50, 162.06, 163,06, 165.35, 181.17, 182.02 ppm; IR ($CDCl_3$) 2960, 2940, 1735, 1650, 1592, 1560, 1455, 1350, 1318, 1220, 1155, 807 cm^{-1}; MS m/e 353, 352, 263, 218, 189, 146, 91; Anal. Calcd for $C_{20}H_{16}O_6$: C, 68.16; H, 4.54. Found: C, 67.94; H, 4.56.

6-[3aR-(3aα,5β,6β,6aα)-3-O-Benzyl-2,2-dimethyltetrahydrofuro[2,3-d]-1,3-dioxolyl]-10a-carbobenzyloxy-7-ethoxy-1,3-dimethoxy-5,8,8a,10a-tetrahydro-9,10-anthracenedione (66)

To a solution of 65 (97 mg, 0.27 mmole) in 4 mL of toluene at 0°C was added 58 (113 mg, 0.32 mmole) in 1 mL of toluene.

The reaction mixture was slowly warmed to ambient temperature and stirred at ambient temperature for 10 h. The solvent was removed in vacuo and the residue filtered through 10 g of silica gel to afford 165 mg (87%) of 66 as a white solid: mp 68-69°C; 300 MHz ^{1}H NMR ($CDCl_3$) δ 1.13 (t, 3 H, J = 6.9 Hz), 1.28 (s, 3 H), 1.46 (s, 3 H), 2.25 (m, 1 H), 2.70 (m, 1 H), 2.95 (m, 1 H), 3.68 (dq, 2 H, J = 6.9 Hz), 3.74 (m, 2 H), 3.85 (s, 3 H), 3.89 (s, 3 H), 4.00 (d, 1 H, J = 3.3 Hz), 4.48 (ABq, 2 H, J_{gem} = 12.3 Hz), 5.04 (ABq, 2 H, J_{gem} = 12.6 Hz), 5.14 (d, 1 H, J = 3.9 Hz), 5.88 (d, 1 H, J = 3.9 Hz), 6.68 (d, 1 H, J = 2.4 Hz), 7.05 (d, 1 H, J = 2.4 Hz), 7.4-7.1 (m, 10 H); IR ($CDCl_3$) 3080, 3060, 3020, 2985, 2930, 1735, 1680, 1590, 1560, 1450, 1365, 1310, 1200, 1155, 1065, 1015, 900, 685, cm^{-1}; MS m/e 698, 581, 533, 478, 397, 343, 107, 91; high-resolution mass spectrum for $C_{40}H_{42}O_{11}$ requires 698.27272, measured 698.27361.

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PART II. SYNTHETIC APPROACHES TO THE 11-DEOXYANTHRACYCLINONES: A FORMAL SYNTHESIS OF AKLAVINONE

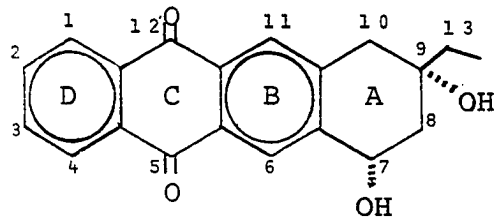
INTRODUCTION

The potent antitumor activity of the 11-deoxyanthracycline class of natural products has stimulated considerable synthetic interest toward their preparation.

This manuscript will detail the results of a program directed toward the total synthesis of aklavinone.

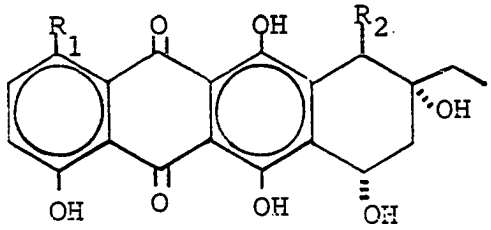
HISTORICAL

The anthracyclines are a growing class of medicinally important antitumor antibiotics originally isolated as colored pigments from soil bacteria. The name anthracycline is due to the structural features associated with these molecules. They are linearly fused tetracyclic compounds containing the anthraquinone chromophore. The general structure and numbering convention of the anthracyclines is shown below.

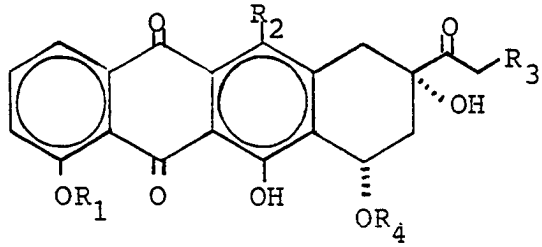


All anthracyclines contain carbohydrate residues in the form of a α-pyranoside linkage which is often located at the C-7 position of the aglycone. The presence of a glycoside linkage is necessary for biological activity, although anthracyclines are isolated in the aglycone form. The aglycones of the anthracycline class are structurally diverse, as are the carbohydrate residues commonly attached. Oxygenation in the basic aglycone structure is usually in the form of phenol, hydroxyl, ketone, or ester functionality. Selected examples of the anthracyclines and aglycones are

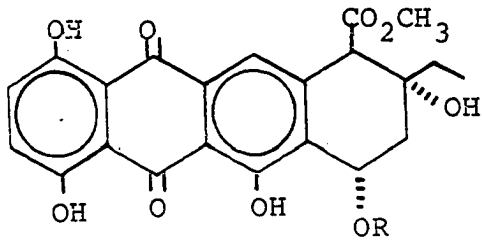
shown below, along with structures of some important L-pyranose sugars.



	R_1	R_2
Rhodomycinones	H	CO_2CH_3 or OH
Isorhodomycinones	OH	CO_2CH_3 or OH

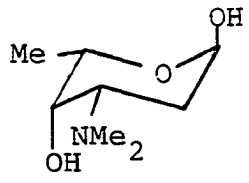


	R_1	R_2	R_3	R_4
Daunomycin	CH_3	OH	H	Daunosamine
Adriamycin	CH_3	OH	OH	Daunosamine
11-Deoxyadriamycin	CH_3	H	OH	Daunosamine
Carminomycin	H	OH	H	Daunosamine

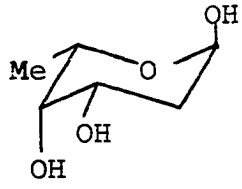


R

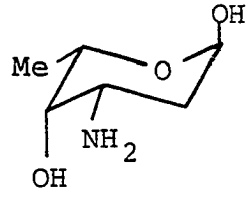
Pyrromycin	Rhodosamine
Cinerubin A	Rhodosamine(α-1,4-)2-deoxy-L-fucose-(α-1,4)-L-cinerulose
Cinerubin B	Rhodosamine(α-1,4)-2-deoxy-L-fucose-(α-1,4-)-cinerulose B.



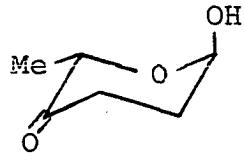
Rhodosamine



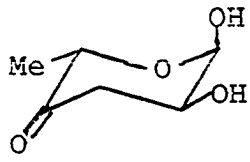
2-deoxy-L-Fucose



Daunosamine



L-Cinerulose



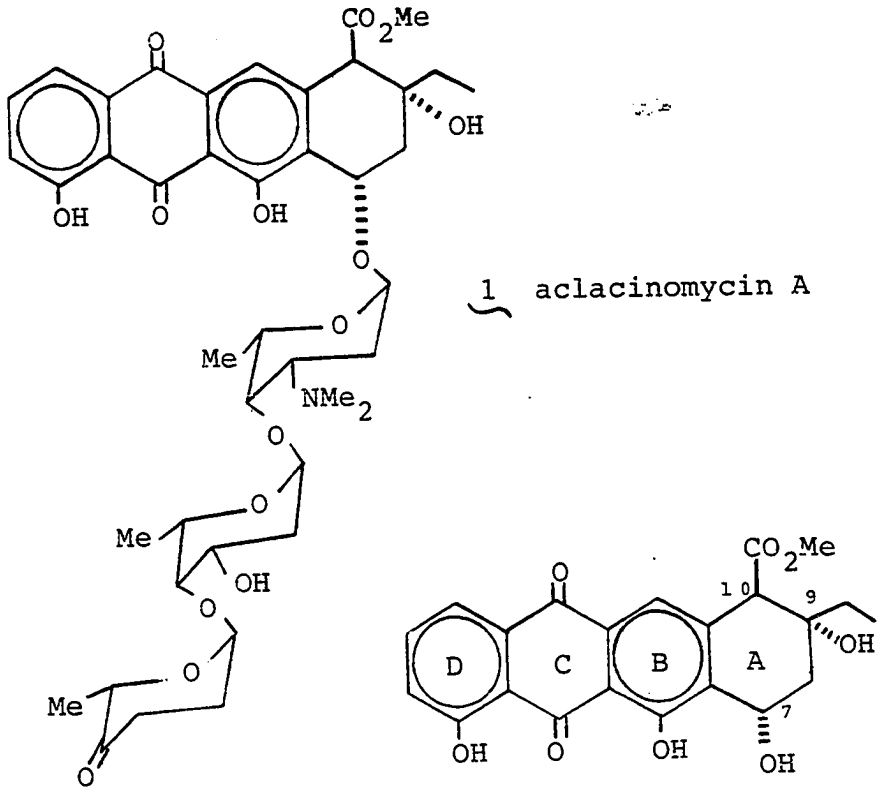
Cinerulose

Daunomycin and adriamycin are first generation anthracycline antitumor agents that have been used in the treatment of a wide variety of human cancers. Daunomycin is

particularly useful in the treatment of mycloblastic and lymphoblastic leukemias (1), while adriamycin is effective against breast and bladder adenocarcinoma, testicular carcinoma, Hodgekin's disease, and acute leukemias (2). Unfortunately, both of these chemotherapeutic agents are also characterized by severe side effects which include immunodepression, gastroenteritis, and cardiac toxicity.

Aclacinomycin A is a second generation anthracycline antitumor antibiotic that was isolated in 1975 by Oki and coworkers from Streptomyces galileus strain MA144-M1 (3). The structure of aclacinomycin A 1 was subsequently elucidated (4) and is shown below. Aclacinomycin A was found to be active against several animal cancers including rat hepatomas, P388 and L1210 leukemias in mice, and Ehrlich ascite tumor. Additionally, aclacinomycin A is 10-15 times less cardiotoxic than the related anthracycline adriamycin (5). More importantly though, it is effective when administered to patients suffering from acute leukemias, malignant lymphoma, and lung, breast, and stomach cancers (6).

The biochemical, pharmacodynamic, and chemical aspects of aclacinomycin A and other anthracycline antibiotics have been studied extensively and are the subjects of several books (6-11) and recent reviews (12-16). The useful clinical applications of aclacinomycin A and advances in the enzymatic glycosidation of aklavinone (2) (17), the aglycone of



1 aclacinomycin A

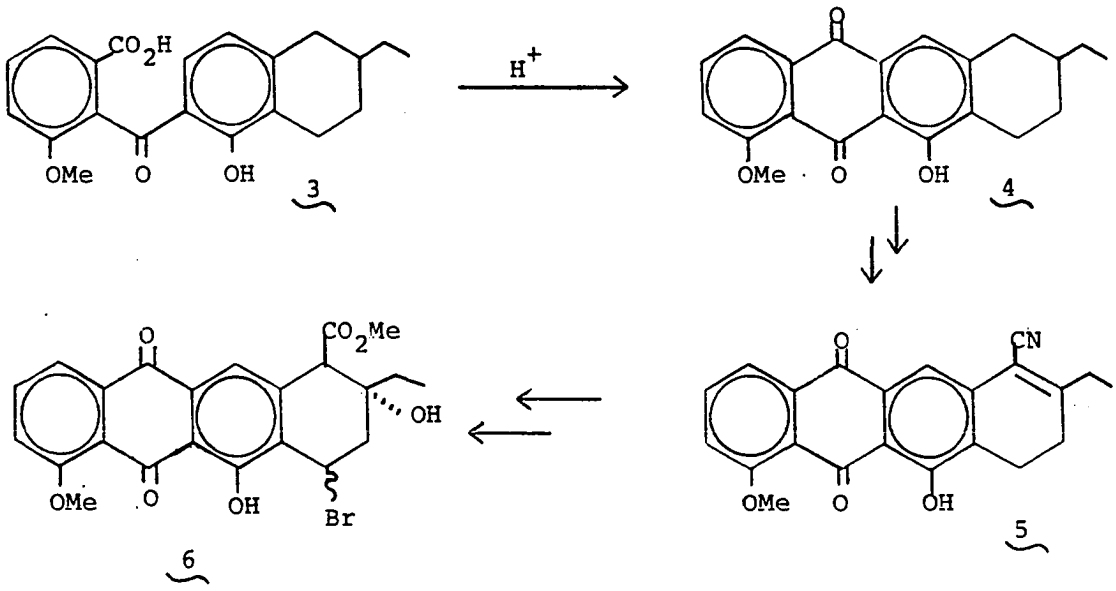
2 aklavinone

aclacinomycin A, has directly influenced the synthetic interests of chemists. Additional impetus for synthetic study toward aklavinone has stemmed from reports of the synthesis of the trisaccharide residue of aclacinomycin A (18) and of its successful chemical coupling with aklavinone (19). This historical will summarize the results of several synthetic approaches to aklavinone and closely related analogs in the 11-deoxyanthracyclinone series.

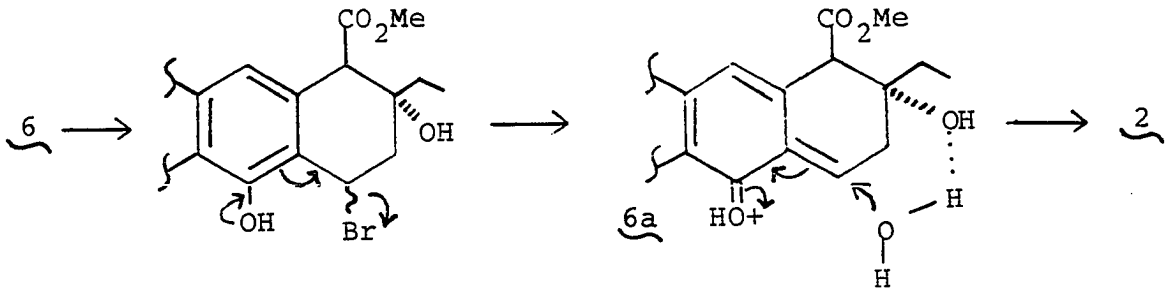
In any synthetic approach to aklavinone, two very important criteria must be satisfied for an efficient

synthesis to ultimately result. The first is the regioselective formation of the tetracyclic system. More specifically, synthetic chemists have employed many different types of reactions including the Diels-Alder cycloaddition, the Friedel-Crafts acylation, and various anionic reactions. Of these, the Diels-Alder reaction has provided the highest degree of convergency in the syntheses of aklavinone. The second challenging aspect encountered in a synthetic approach to aklavinone is the stereospecific introduction of the C-7 hydroxyl function. This requirement has been met by a stereocontrolled benzylic bromination/solvolysis sequence that has been used in virtually every synthesis of aklavinone.

Two of the early syntheses of aklavinone were based upon Friedel-Crafts ring closure methodology. Confalone and Pizzolato were responsible for a D + BA route in 1981 (20). Compound 3, the product of an ortho-specific Lewis acid catalyzed Fries rearrangement, underwent cyclization under the influence of boric acid-sulfuric acid to provide the anthraquinone 4 in 57% yield. Anthraquinone 4 was elaborated in a lengthy sequence to nitrile 5. Epoxidation, hydrolysis of the nitrile, stereospecific hydrogenolysis of the epoxide, and benzylic bromination provided 6 in low overall yield from nitrile 5. Solvolysis of bromide 6 was stereospecific, presumably via the protonated enone 6a, to afford racemic

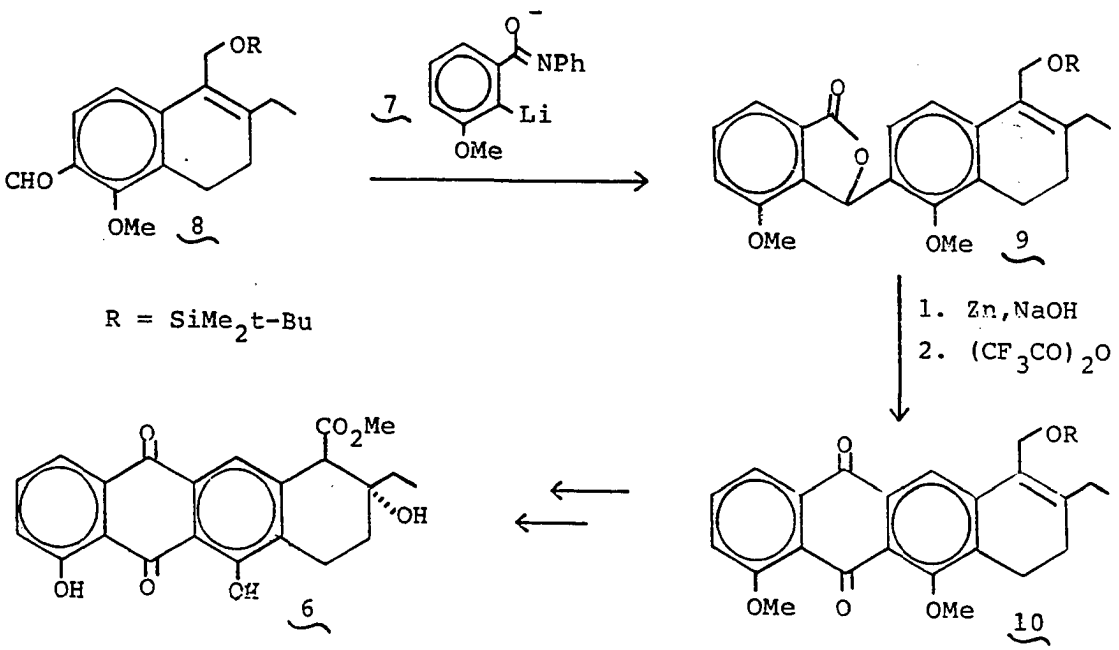


aklavinone by hydration directed by the hydroxyl function at C-9.



Although the Confalone synthesis was regio- and stereo-controlled, the overall yield of aklavinone was low. A more convergent synthesis, also of the D + BA type, was subsequently reported by Kende and Rizzi (21). Addition of the ortho-metallated carboxamide 7 to the highly functionalized aldehyde 8 produced the phthalide 9 in high yield.

Hydrogenolysis of the phthalide and Friedel-Crafts ring closure provided the anthraquinone 10 in 60% yield after aerial oxidation.

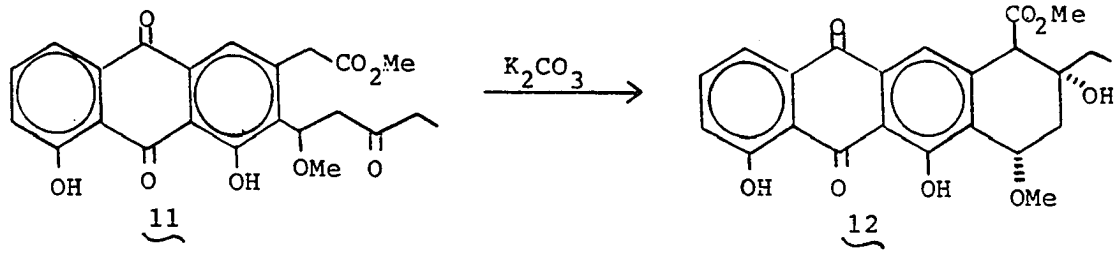


Elaboration of 10 to the aklavinone intermediate 6 and thence to racemic aklavinone was accomplished by reactions similar to those used in the Confalone synthesis.

While only two successful approaches to aklavinone have involved Friedel-Crafts ring closure methodology, no fewer than six synthetic routes involving carbanionic intermediates in carbon skeletal preparation have been published. The anionic pathways can be further subdivided into approaches involving aldol-type condensations, phthalide annulations, and

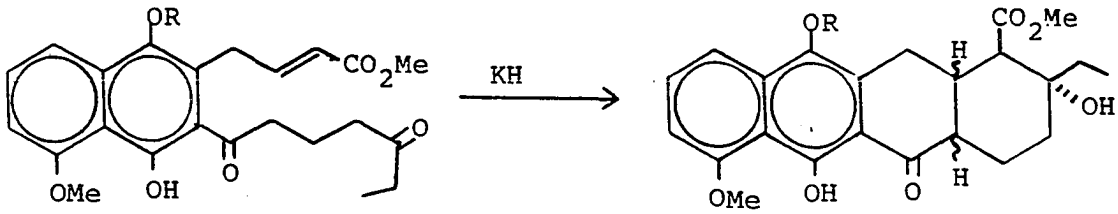
vicarious nucleophilic aromatic substitution. Synthetic approaches involving aldol-type condensations will be covered first.

The intramolecular aldol condensation has been an important strategy in the syntheses of aklavinone. One of the first syntheses of aklavinone was based largely on this approach (22). Treatment of ketoester 11 with potassium carbonate afforded a mixture of diastereomeric aldol products with the correct isomer 12 as a minor product in 36% yield.



Fortunately, all of the isomers could be equilibrated to the desired relative stereochemistry by a combination of acidic and basic treatments to provide 12 in approximately 60% yield after two equilibrations. Although little stereocontrol was obtained in the cyclization, this is the only synthesis of aklavinone in which functionality at C-7 is intact prior to the construction of the tetracyclic system. Furthermore, this route has been extended to an asymmetric synthesis of aklavinone (23). An analogous intramolecular condensation was later reported by Krohn (24).

A similar approach was used by Marayuma and coworkers; however, both the A and B rings were formed by a tandem Michael addition-aldol condensation (25). Thus, 13 underwent biscyclization upon treatment with potassium hydride in the presence of a [2.2.2] cryptand to provide 14. In this



13

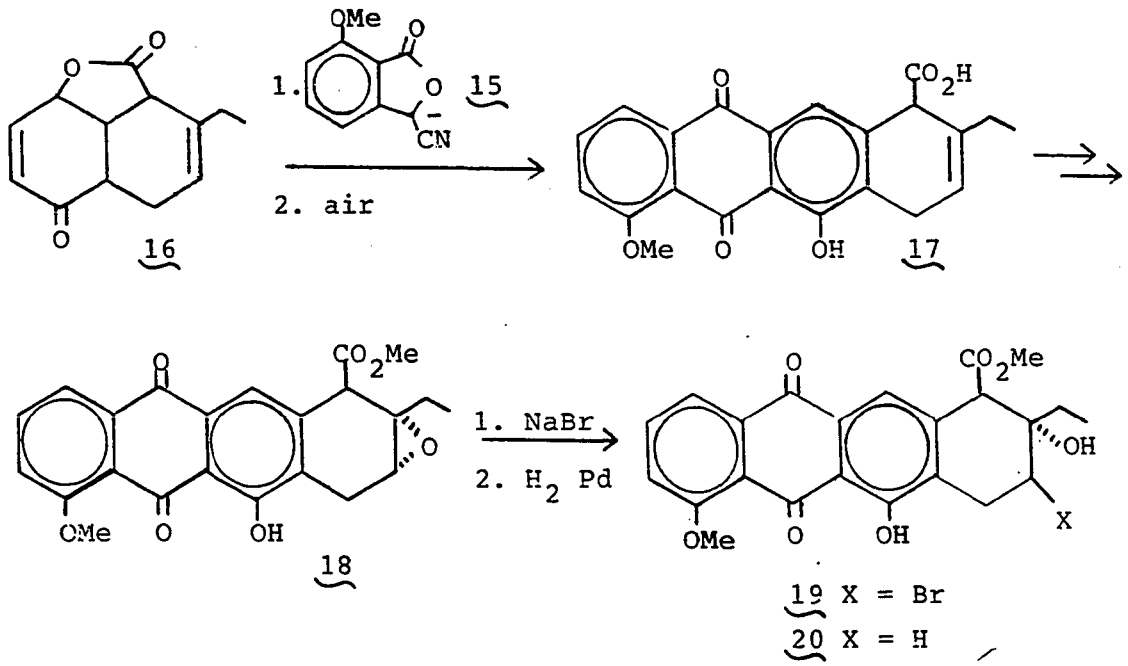
R = $SiMe_2t$-Bu

14

biomimetic reaction, the presence of the crown ether was essential to the obtention of a favorable mixture of diastereomers at C-9 and C-10.

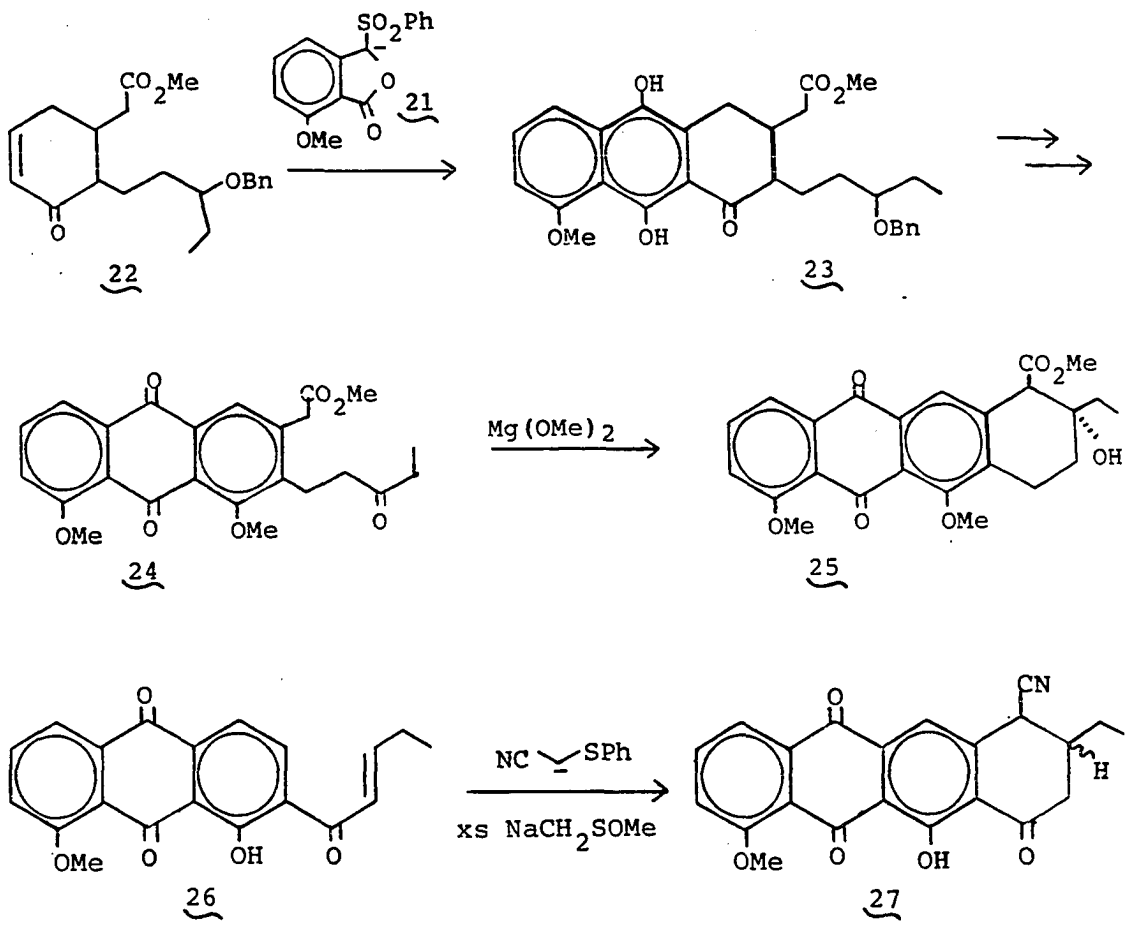
In 1981, Li and Wu reported a stereospecific and convergent synthesis of aklavinone (26). In this route, cyanophthalide anion 15 reacted with the elaborated enone 16 to afford anthraquinone 17 in good yield after aerial oxidation. Conversion of 17 to the aklavinone precurser 20 involved a stereoelectronically controlled epoxide ring opening of 18 and hydrogenation of the resulting bromide.

A general synthesis similar to that shown above was recently reported by Hauser and Mal (27). Phthalide annulation between sulfone 21 and cyclohexenone 22 provided



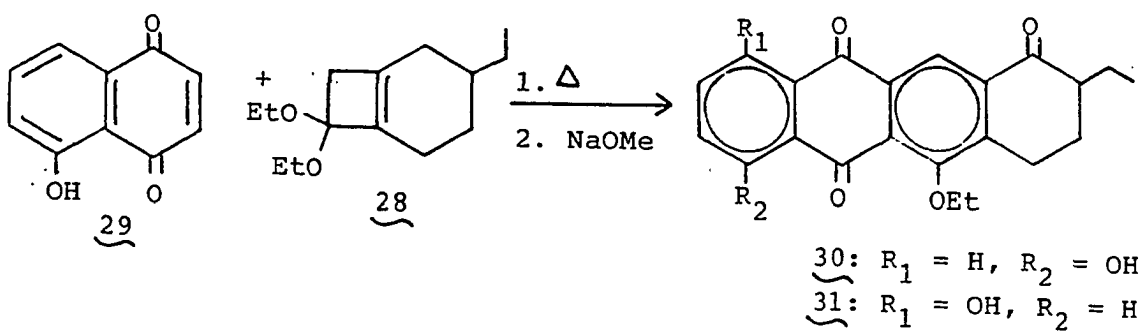
the naphthalenone derivative 23 in excellent yield. Following a four step conversion of 23 to 24, treatment of 24 with magnesium methoxide effected an intramolecular aldol condensation to provide 25 in 70% yield. As expected, significant amounts of the diastereomeric product were also produced.

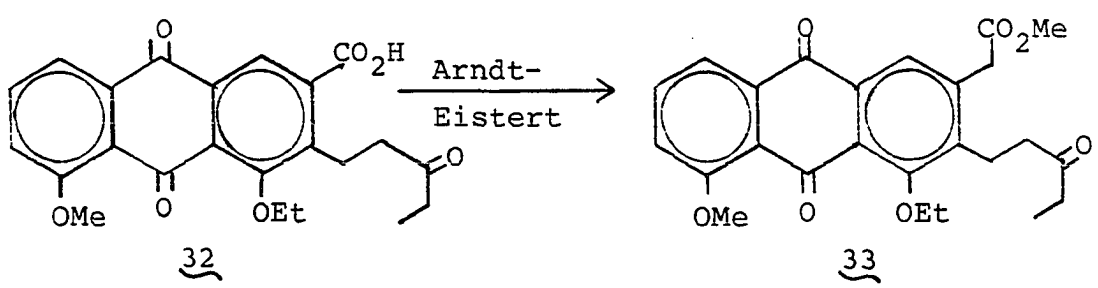
One of the first synthetically useful examples of a vicarious nucleophilic aromatic substitution was reported by Murphy and Cara (28). In their approach to aklavinone, the enone 26 reacted with the preformed anion of the acetonitrile derivative to provide the aklavinone precurser 27 in good yield.



Presumably, the phenylthioacetonitrile anion undergoes Michael addition to the enone, followed by vicarious substitution onto the anthraquinone moiety, and finally, expulsion of thiophenoxide. Although 27 closely resembles the Confalone intermediate 5 (vide supra), no reports on its ultimate conversion to aklavinone have appeared in the literature.

The final strategy to be discussed is the Diels-Alder approach. As in the case of the phthalide annulation methodology, the tetracyclic skeleton is amenable to a highly convergent DC + BA strategy. Boeckman and Sum have employed this strategy in the form of a naphthoquinone-vinylketene-acetal cycloaddition (29). Thus, heating cyclobutane 28 in the presence of juglone 29 produced two separable anthraquinones 30 and 31 in a ratio of 4.4:1. Unfortunately, direct

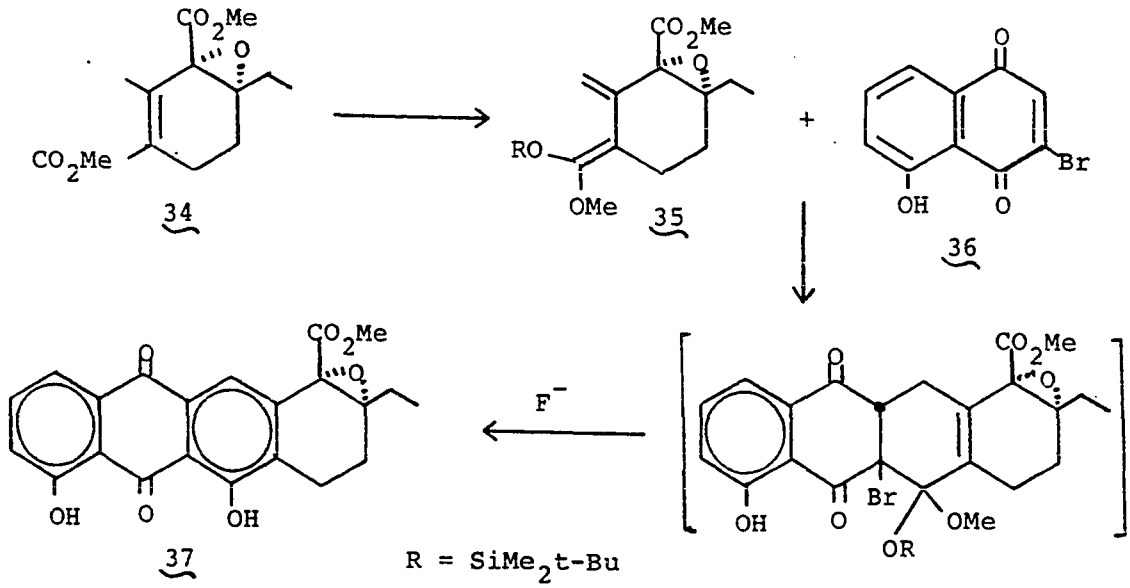




conversion of the major regioisomer 30 to aklavinone proved troublesome. Ultimately, Arndt-Eistert homologation of an A-ring cleavage product 32 produced 33 which was transformed

to aklavinone by an intramolecular aldol condensation identical to that seen in Hauser's work (vide supra). A similar vinyl ketene acetal cycloaddition-ring-cleavage route was also reported by Gesson and coworkers (30) in their synthesis of auromycinone, a C-9 methyl analog of aklavinone.

A related approach was later published by Bauman, Hawley, and Rapoport which judiciously utilized preexisting ketene acetal functionality for an expedient conversion of the Diels-Alder adduct to aklavinone (31). Deprotonation of 34 and silylation produced 35. Without purification, 35 underwent cycloaddition with the bromojuglone derivative 36 to afford 37. In this case, in situ elimination of HBr and the silyl group produced the aromatic B-ring.



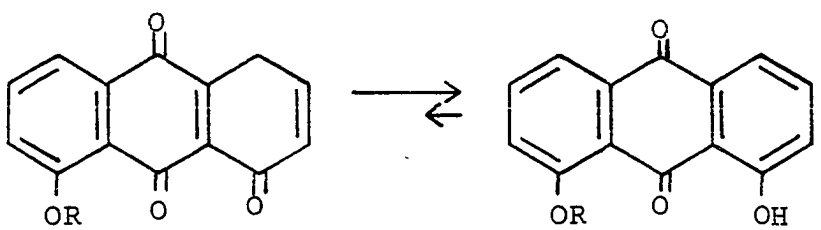
Compound 37 is easily transformed to aklavinone using the previously defined procedures of Confalone and Kende (vide supra). The Rapoport synthesis provides an excellent example of regiocontrol in formation of the tetracyclic skeleton of aklavinone. Considering the Diels-Alder reaction, the combined polarizing effects of the bromine and peri-hydroxyl group in 36 resulted in the exclusive formation of the correct regioisomer. This, coupled with the ease in preparation of a variety of bromojuglone derivatives (32), makes the vinyl ketene acetal cycloaddition route applicable to the synthesis of a wide variety of anthracyclinones with A-ring substitution similar to aklavinone.

In summary, 11-deoxyanthracyclinones such as aklavinone are a valued group of antitumor agents. Their clinical efficacy in conjunction with their reduced side effects has made them valuable targets for the synthetic chemist. Synthetic approaches involving the Friedel-Crafts reaction, anionic reactions, and the Diels-Alder cycloaddition have been used for their construction. While the anionic approaches have provided the highest degree of regiochemical control, the Diels-Alder pathways are the most direct. Nearly every approach has involved a benzylic bromination/solvolysis sequence to introduce the C-7 hydroxyl function. Although

this sequence provides adequate stereocontrol, alternative methods for A-ring functionalization and carbon skeleton construction are needed.

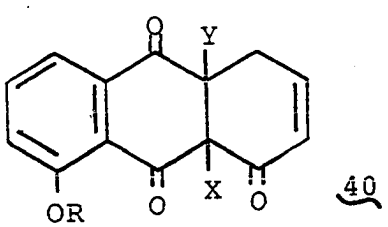
RESULTS AND DISCUSSION

Our approach to aklavinone was initiated during the course of our synthetic studies toward olivin, the aglycone of the aureolic acid antibiotic olivomycin A (part I). We envisioned enone 38 as a potential DCB ring system synthon. A Diels-Alder cycloaddition with a suitably functionalized diene at the non-quinonoid olefin of 38 would produce a precurser to aklavinone with much of the functionality of the A-ring intact.



38 39

Unfortunately, even if 38 could be prepared, it would rapidly tautomerize to the anthraquinone 39. An attractive equivalent to 38 in which either X or Y blocks aromatization to the anthraquinone represented an interesting alternative.



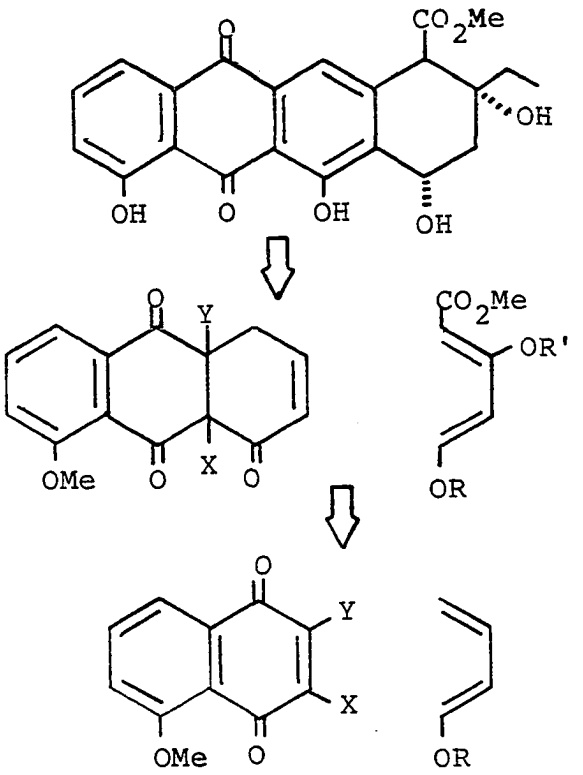
40

In the case of 40, no ambiguity regarding the site selectivity of the Diels-Alder reaction would be present. Furthermore, if X and Y were functional groups that could be readily removed, a controlled avenue for aromatization of the B-ring at some later stage would be possible. Finally, a route involving enone 40 as a dienophile would avoid the familiar bromination/solvolysis sequence to introduce the hydroxyl group at C-7.

A requirement of 40 would be its preparation in a regiospecific manner. Based on our findings in the olivin study, we anticipated that it would be available from a Diels-Alder reaction of an activated naphthoquinone derivative. Our retrosynthetic analysis for aklavinone based on the concept of a blocked anthraquinone tautomer is summarized in Scheme I.

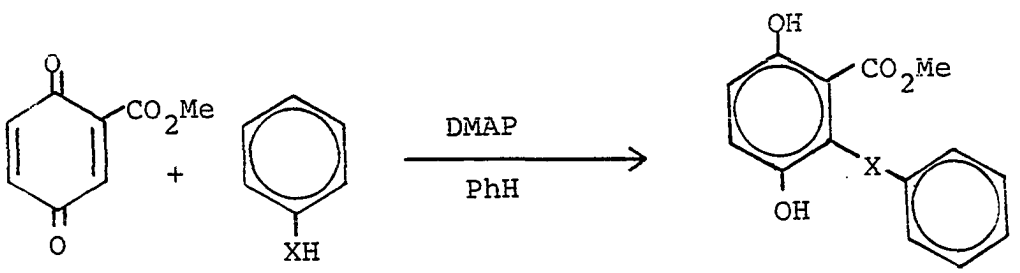
For our model studies we desired as an activating group, X, a methyl ester. Since sulfides are easily removed by a variety of methods, the phenylthio group was chosen as the blocking functionality, Y. Introduction of a phenylthio group via conjugate addition of benzenethiol to 2-carbomethoxy-1,4-naphthoquinone had precedent in the p-benzoquinone series. Müller and coworkers studied the addition of a variety of nucleophiles to carbomethoxy-p-benzoquinone (33). High yields of the hydroquinone addition products were obtained when pyridine derivatives were employed as catalysts.

Scheme I.



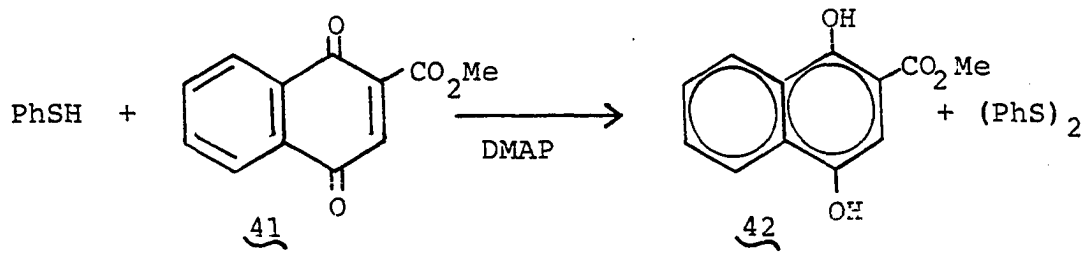
X = an electron withdrawing group

Y = a stable blocking group



X = S, NR, O

In the event, treatment of 2-carbomethoxy-1,4-naphthoquinone (41) (34) with benzenethiol in the presence of dimethylaminopyridine (DMAP) resulted in a rapid reaction. Upon workup however, only the naphthhydroquinone 42 and diphenyldisulfide were isolated. Clearly, an oxidation-reduction reaction had occurred.

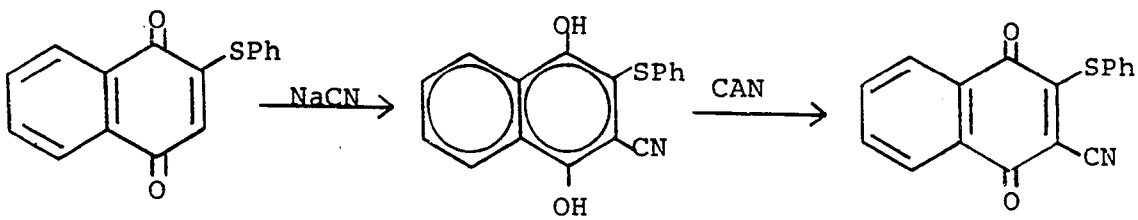


41 42

Employing a full equivalent of DMAP or using the sodium salt of benzenethiol led to identical results. Use of Lewis or protic acid catalysis in hopes of further activating the quinone toward nucleophilic addition also failed. Apparently, the stabilizing effect of the annulated benzene ring slowed the rate of nucleophilic addition to the quinone, allowing electron-transfer to become the dominant reaction pathway.

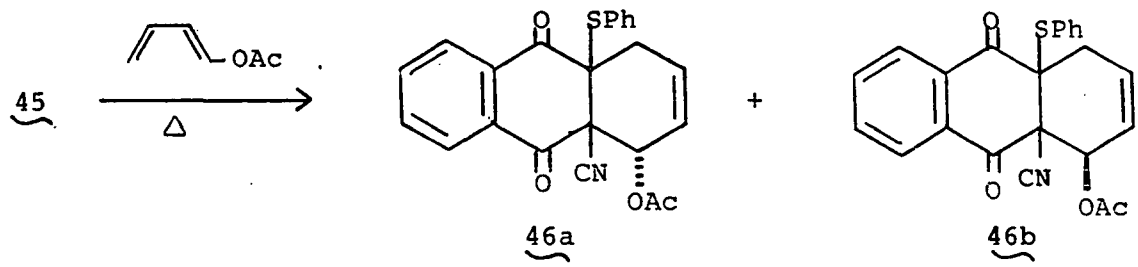
In light of these results we elected to reverse the order of addition of functionality to the naphthoquinone moiety. Since Kolbe-Schmitt carboxylation (35) of a phenylthio-naphthoquinone followed by esterification and oxidation was viewed as awkward and low yielding, the nitrile function was considered as a substitute for the ester. Although cyanide

additions to aryl-substituted naphthoquinones were known, it was by no means a general reaction (36). Nevertheless, treatment of 2-phenylthionaphthoquinone (43) (37) with sodium cyanide in a four component aqueous solvent system produced the cyanonaphthalene derivative 44 in 94% yield. Oxidation to the corresponding naphthoquinone 45 was accomplished in high yield with ceric ammonium nitrate (CAN) in aqueous acetonitrile (38). Thus, the DC portion of the model blocked anthraquinone tautomer was available in approximately 75% overall yield beginning with commercially available 1,4-naphthoquinone.



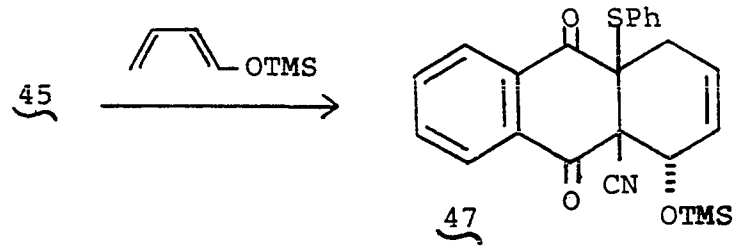
43 44 45

We next investigated the Diels-Alder behavior of quinone 45. Treatment of 45 with excess 1-acetoxy-1,3-butadiene at 130°C for 20 hours produced a 2.5:1 mixture of "endo" and "exo" Diels-Alder adducts respectively. The two products were easily separated by fractional crystallization. That the major Diels-Alder product 46a was the "endo" isomer was evident from its ^{1}H NMR spectrum. The methyl group of the allylic acetate appeared at 1.17 ppm; strongly shielded in

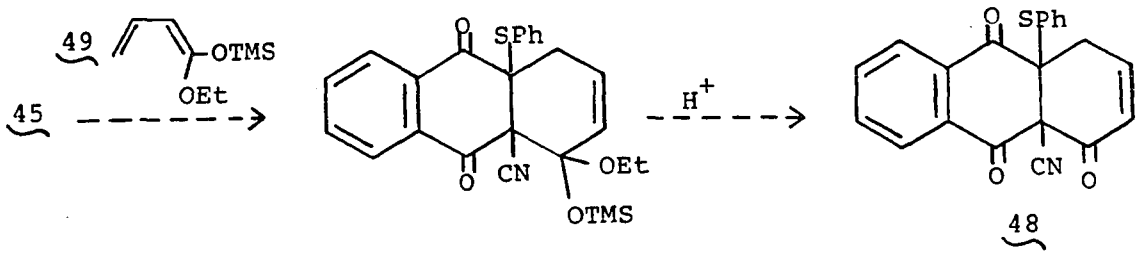


comparison to the same protons of the "exo" isomer which appeared at 2.11 ppm. This exceptionally high-field shift of the axial acetate results from a conformation placing it directly below the aromatic ring (39). Similarly, the axial methine proton of 46b also exhibits a ring current shielding, albeit only a 0.20 ppm shift (40).

The Diels-Alder reaction of 45 with 1-trimethylsilyloxy-1,3-butadiene (41) required only a few hours at 80°C for completion. Adduct 47, the only product formed, was isolated by direct crystallization of the crude reaction product in over 95% yield. In this example, only the "endo" isomer was formed as evidenced by a singlet appearing at -0.35 ppm for the trimethylsilyloxy group.



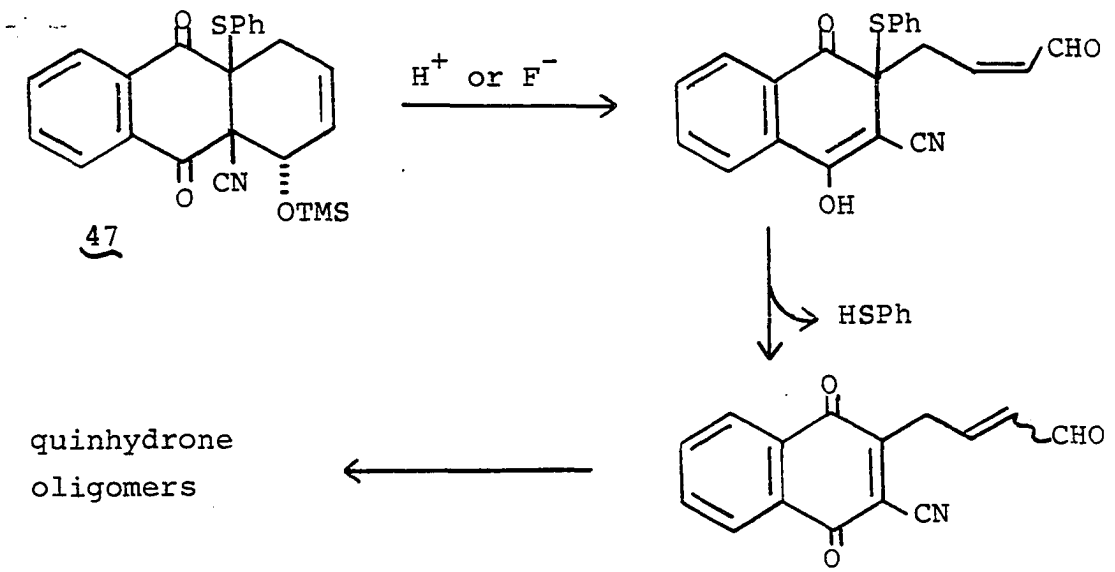
Reacting 45 with mixed vinyl ketene acetal 49 (42) produced no Diels-Alder adduct and only intractable tars at room temperature. Identical observations were made when the ketene acetal was added to a solution of the quinone at -78°C. Independent results from these laboratories indicate that electron transfer or a similar ionic pathway intervenes in Diels-Alder reactions of 49 with activated quinones (43). Had



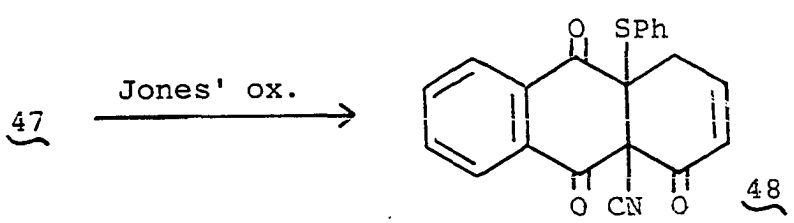
this reaction been successful, a simple hydrolysis reaction would have provided the DCB synthon 48.

An alternative sequence involving desilylation of 47 followed by oxidation was next examined. Unfortunately, under a variety of reaction conditions commonly used to cleave silyl groups, decomposition to a purple solution was observed. The ^{1}H NMR spectra of the crude reaction products indicated a facile retro-aldol reaction was occurring (Scheme II). Apparently, the cyano group, with its strong inductive effect facilitated cleavage adjacent to the allylic alcohol. Ultimately, quinhydrones, which are highly colored quinone-hydroquinone complexes, were produced (44).

Scheme II



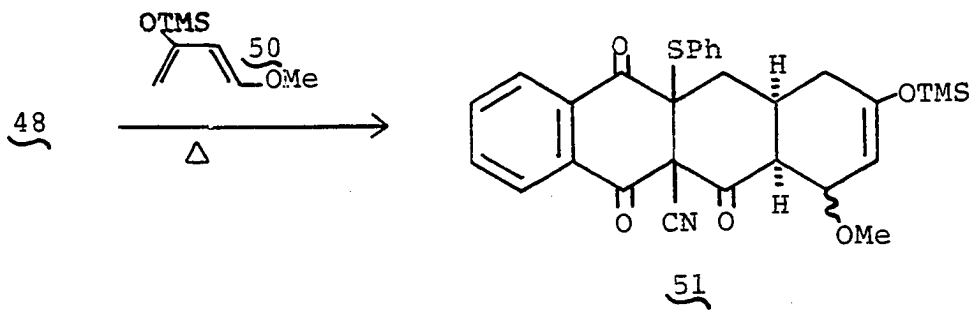
We were pleased to find that direct oxidation of the silyl ether 47 with the Jones' reagent in acetone produced the requisite enone 48 in high yield. Evidently, protiodesilylation under the acidic conditions produced an



allylic alcohol which was oxidized at a much faster rate than the destructive retro-aldol reaction described above (45). Although 48 was similarly sensitive to traces of acid or base, it was easily purified by crystallization from anhydrous

diethyl ether. In this way, multigram quantities of 48 were available in 60-65% yield from napthoquinone 45.

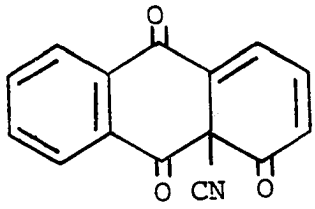
Having established a high-yielding route to 48, we next investigated the crucial Diels-Alder reaction that would append the A-ring to the blocked anthraquinone tautomer. Reaction of 48 with diene 50 (46) at 110°C for 24 hours produced 51 as a mixture of "exo" and "endo" isomers in low yield accompanied by substantial amounts of unidentified polar materials. Unfortunately, the cycloaddition was not



51

reproducible and in many instances failed completely. In addition to the low yield obtained, hydrolysis of the β-methoxy silyl enol ether resulted in extensive A-ring aromatization and retro-aldol cleavage of the B-ring (47).

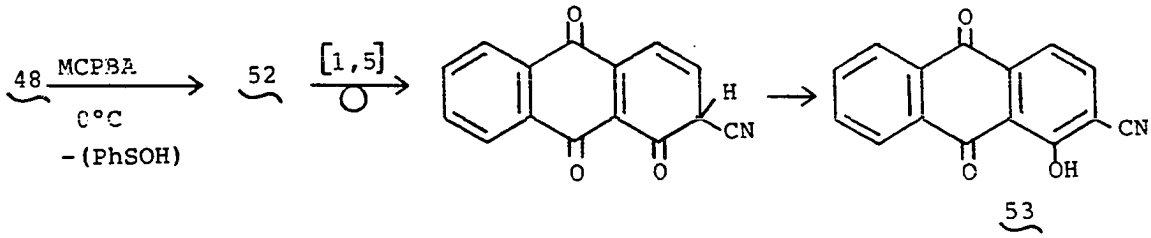
As a possible solution to these problems, we considered dienone 52 as an alternative dienophile. Dienone 52, by virtue of its increased planarity, was expected to be more reactive than 48. The presence of an olefin in the B-ring of a Diels-Alder product of 52 would allow for an *in situ*



52

vinylogous elimination of HCN, and thus solve the problem of B-ring cleavage.

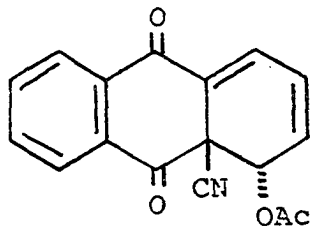
To prepare 52, we envisioned oxidation of 48 to the sulfoxide followed by pyrolytic cis-elimination of benzenesulfenic acid (48). In the event, oxidation of 48 with meta-chloroperbenzoic acid (MCPBA) was rapid at 0°C. Upon workup however, the unexpected anthraquinone 53 was isolated in high yield! Apparently, oxidation was followed by immediate sulfoxide elimination to produce 52 (49). Dienone 52 must undergo a [1,5] suprafacial carbon shift, tautomerization then provided 53.



53

A literature search revealed that facile rearrangements such as this are not uncommon in "blocked aromatic"-cyclohexadienone systems (50-52). It is interesting to note

that 54, prepared from 46a by an analogous oxidation-sulfoxide elimination sequence, was completely stable and did not decompose until heated to its melting point. Clearly, formation of the anthraquinone accompanied by aromatization provides considerable driving force for this rearrangement.

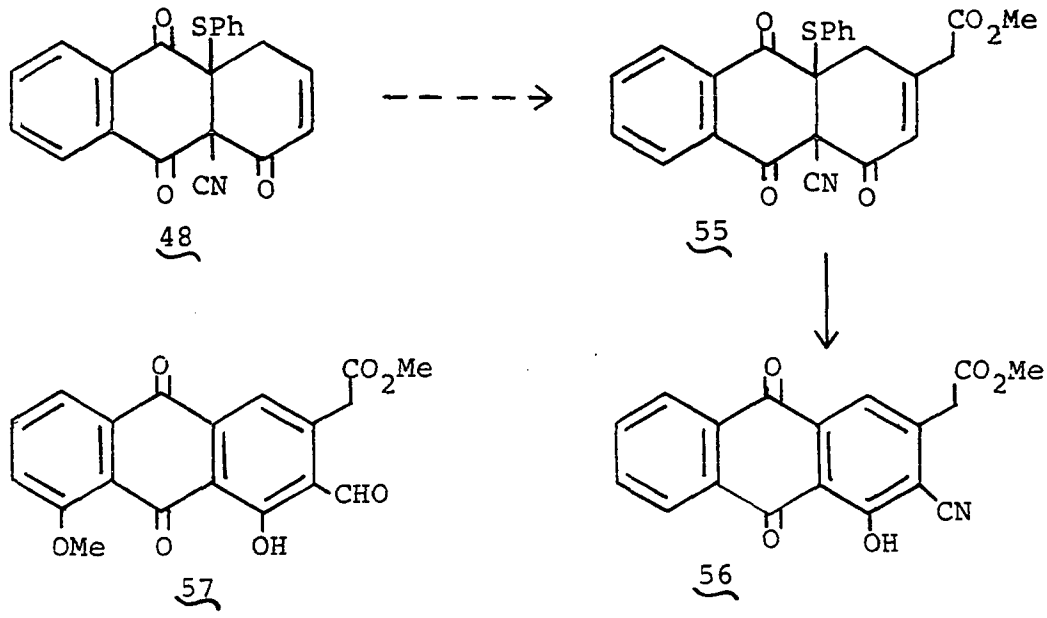


54

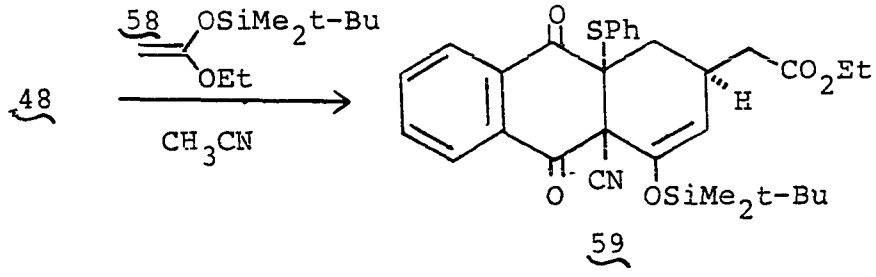
Although it was disappointing that neither 48 or 52 could be used for direct attachment of the A-ring, the facile [1,5] nitrile shift was viewed as a synthetically useful reaction. If an acetic ester residue could be incorporated into 48 as shown (Scheme II), sulfoxide elimination would provide 56 after the nitrile transfer. A similar intermediate, 57, had been employed by Kishi in his elegant synthesis of aklavinone (22).

Realizing that conjugate addition of an acetate ester enolate to 48 would fail due to its extreme base sensitivity, an alternative mode of addition that would occur under neutral conditions was sought. The Tamura addition of silyl ketene acetals (53) served this need admirably. Reaction of 48 with

Scheme III



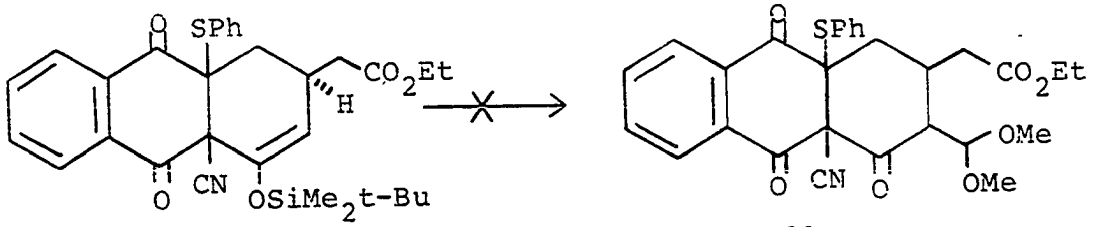
the mixed ketene acetal 58 (54) in anhydrous acetonitrile at 45°C produced ester 59 in 62% yield.



The 300 MHz-^{1}H NMR spectrum of 59 exhibited an eight line AB quartet of doublets for the methylene protons adjacent to the ester and a sharp doublet at 4.96 ppm (J = 3.1 Hz) for the olefinic enol ether proton.

Dehydrogenation of 59 to the corresponding enone 55 proved impossible. Attempts with palladium(II) acetate (55), dichlorodicyanobenzoquinone (DDQ) (56), and triphenylcarbenium tetrafluoroborate/collidine (57) all returned unreacted enol silyl ether. Apparently, the pseudo-axial methine proton, which is located on the concave face of 59, is far too hindered for abstraction by these reagents.

We next investigated electrophilic additions of formyl cation equivalents to 59. If successful, removal of the nitrile and thiophenyl groups followed by B-ring aromatization would provide an advanced intermediate in the Kishi synthesis. Treatment with trimethyl orthoformate under the Noyori conditions (58) failed to produce any of the desired β-keto acetal 60. Treatment with dithienium tetrafluoroborate (59) also failed, returning the enol ether unscathed.

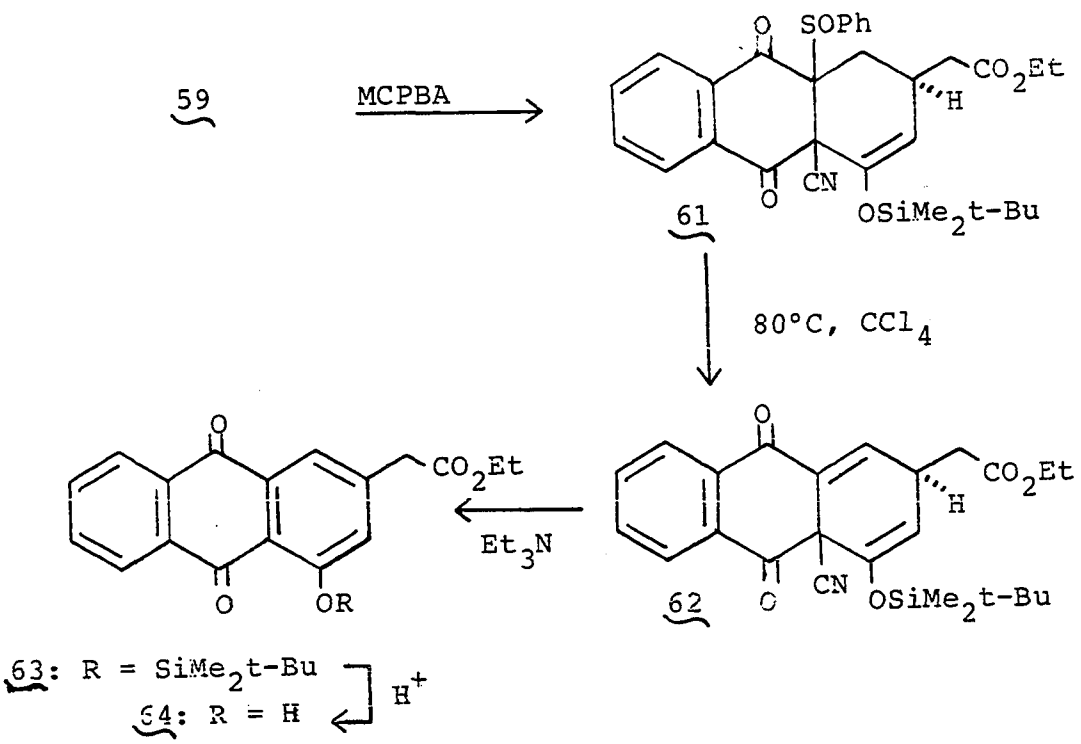


59 60

In light of these results, it was not surprising that N-bromosuccinimide (NBS) (60) and phenylselenenyl chloride (61), reagents known to react well with silyl enol ethers, also failed to provide any addition products. At this point,

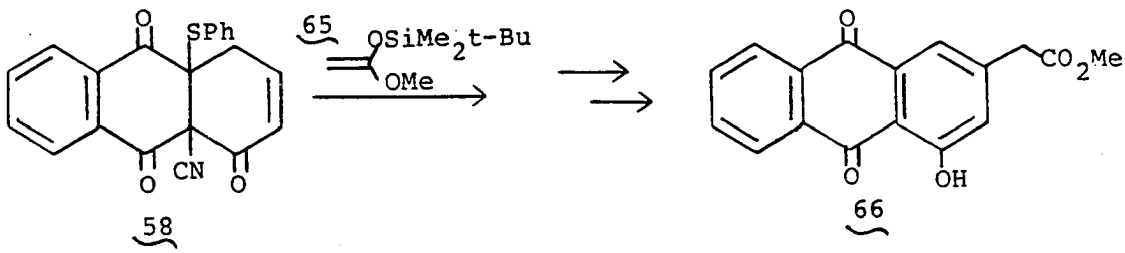
convincing rational for the unreactive enol ether is lacking. The low reactivity cannot be purely steric in nature. Since the thiophenyl and acetic ester groups occupy pseudo equatorial positions, they should not severely interfere with electrophilic addition to the enol ether site.

Taking full advantage of the unyielding enol ether group, treatment of 59 with MCPBA cleanly and selectively produced the sulfoxide 61 as a 2.5:1 mixture of diastereomers in 98% yield. Heating the isomers to 80°C effected syn-elimination to provide diene 62 in 88% yield. This result was surprising



since elimination of HCN to afford the anthraquinone 63 should have been rapid.

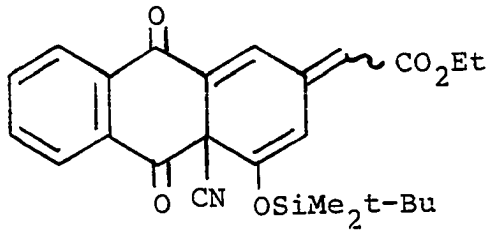
Diene 62 did eliminate HCN on treatment with triethylamine to produce 63. Without purification, 63 was hydrolyzed with aqueous HCl to produce 64 in good overall yield from 62. For simplification of the NMR spectra of these intermediates and for literature comparison of physical data, the corresponding methyl ester of 64 was prepared. Substituting 1-methoxy-1-(tert-butyldimethylsilyloxy)ethylene 65 for 58 in the Tamura reaction, and under essentially identical reaction conditions,



66 was obtained. Compound 66 was identical in every respect with the compound prepared by Krohn et al. (62).

The obtention of 62 allowed for a reinvestigation of the nitrile shift approach to aklavinone. Due to its increased planarity, dehydrogenation of 62 was anticipated to occur because the methine proton was no longer sterically shielded as in 59 (vide supra). Indeed, dehydrogenation with DDQ produced a new product. However, NMR analysis of the product was only consistent with the formation of triene 67.

Apparently, nucleophilic attack on silicon by the DDQ

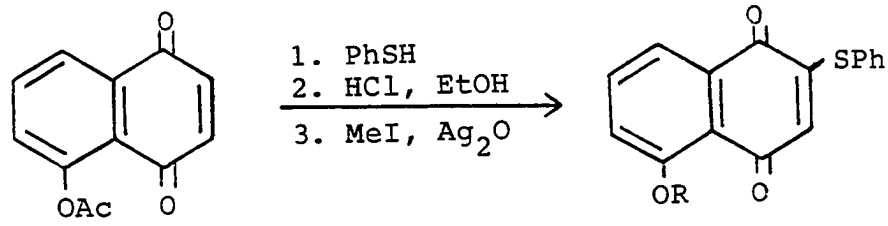


67

hydroquinone anion was not favorable, and only elimination of a proton from the presumed cationic intermediate resulted (63). Finally, addition of formyl cation equivalents to 62 failed, returning unreacted diene.

Model studies were suspended at this point in favor of a formal total synthesis of aklavinone. In order to achieve this goal, a methoxyl group at C-8 of 45 (naphthoquinone numbering) was necessary. Given that this compound could be readily prepared, an intermediate in the Kishi synthesis would be available by repetition of the reactions used to prepare 64.

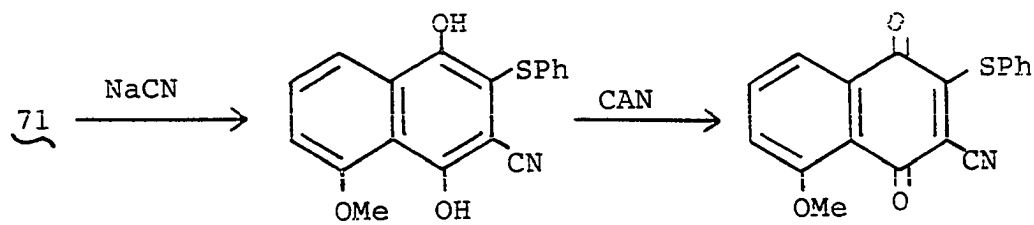
Toward this end, treatment of juglone acetate (68) (64) with benzene thiol produced quinone 69 in 80% yield (65). The literature report indicated that this reaction was completely regioselective. In our hands, a 97:3 ratio of the desired 2-phenylthionaphthoquinone and its 3-phenylthio isomer were



68

69: R = Ac
70: R = H
71: R = OMe

indicated by ^{1}H NMR analysis at 300 MHz. Fisher transesterification followed by methylation (66) produced naphthoquinone 71 in high yield. In the course of the latter two steps, the contaminating isomer was easily removed by crystallization. Cyanide addition to 71 was complicated by slow aerial oxidation of the hydroquinone product. Thus, the crude addition product was treated without purification with CAN to produce the desired 3-cyanonaphthoquinone 72 in 92% yield.

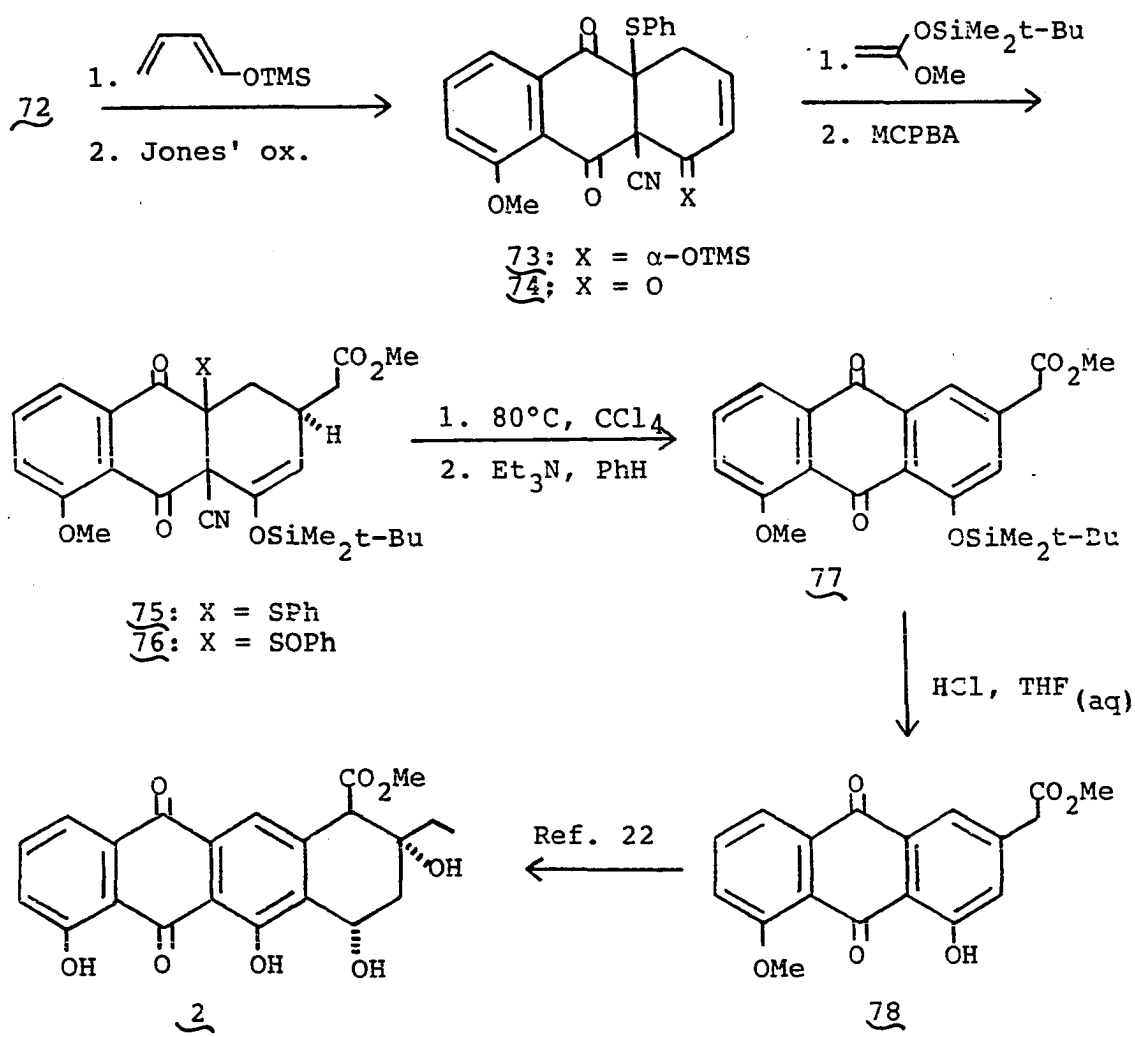


72

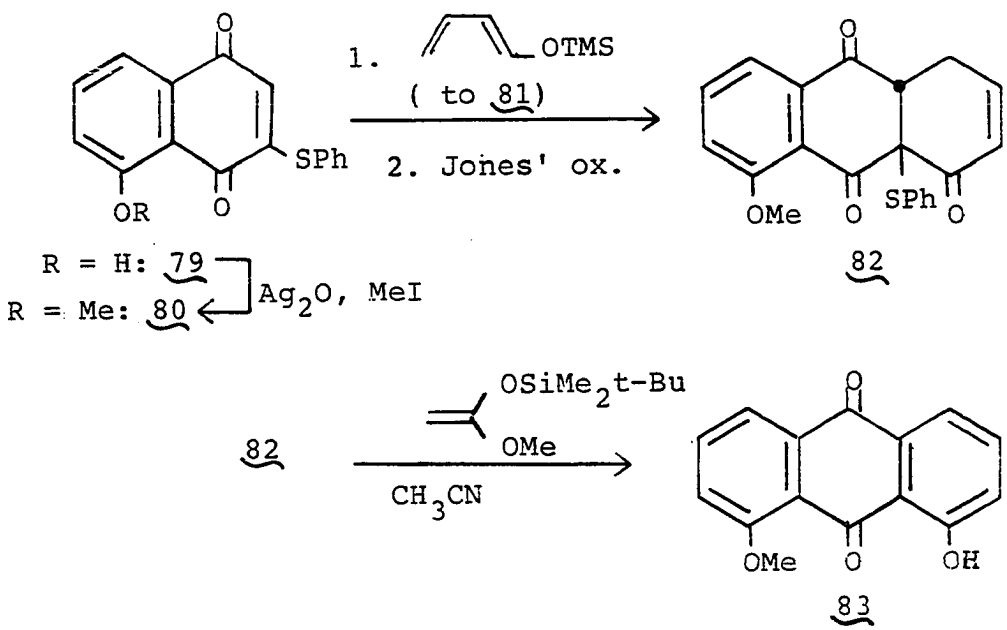
The remainder of the formal synthesis closely paralleled that of the deoxy-compound, and is shown in Scheme IV. Diels-Alder cycloaddition of 72 with 1-trimethylsilyloxybutadiene occurred in 90% yield to produce 73 which was oxidized in 88%

yield to afford enone 74. Ketene acetal addition and oxidation produced sulfoxide 76 as a 3:1 mixture of diastereomers. Without purification, the diastereomers were heated to effect cis-elimination. Elimination of HCN provided anthraquinone 77. Finally, hydrolysis of 77 with HCl in aqueous THF produced the desired anthraquinone 78. Thus, an operationally convenient and direct route to the DCB subunit of aklavinone was achieved (67).

Scheme IV

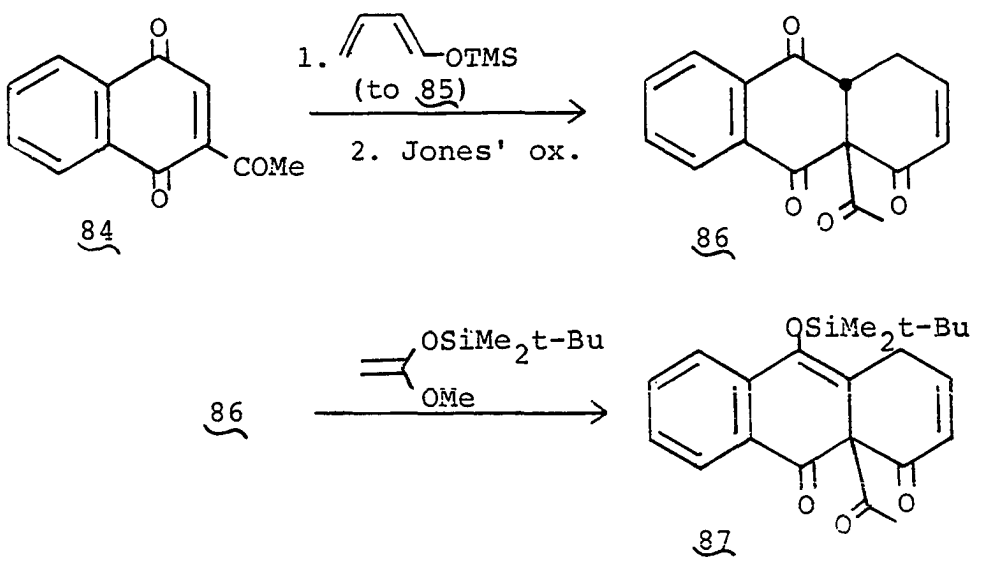


In principle, only one substituent should be required to prevent tautomerization to an anthraquinone. To test this, a direct synthesis of 82 from the known 3-phenylthiojuglone 79 (65) was developed. Diels-Alder cycloaddition of 80 proceeded



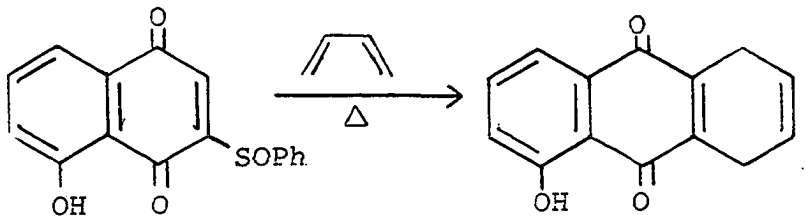
with high regioselectivity, and by ^{1}H NMR analysis, only the "ortho" product was detected. Jones' oxidation of the resulting Diels-Alder adduct 81 afforded 82 in high yield. However, when enone 82 was reacted with the ketene acetal under conditions which were previously successful, only 1-hydroxy-8-methoxyanthraquinone 83 was isolated. Despite several modifications (68) including an attempt at 7 kbar pressure (69), only decomposition of 82 to 83 was observed.

A similar system wherein the acetyl group served as a blocking function was also prepared. In this system, elimination and aromatization were considered unlikely. Thus, 2-acetylnaphthoquinone 84 (70) underwent a facile Diels-Alder reaction to provide 85 in excellent yield. Desilylation and Jones' oxidation then afforded 86. Surprisingly, when treated with the ketene acetal, 86 was silylated to produce 87. Additionally, Diels-Alder attempts with 86 and a variety of dienes failed, returning unreacted 86.



Despite the well-known electron-withdrawing effect of the sulfoxide group, and the use of vinyl sulfoxides as dienophiles, only two reports on the use of sulfinyl quinones in Diels-Alder reactions have appeared (71). One report originating from these laboratories indicated that

naphthoquinones monosubstituted with the sulfoxide group at the 2-position are powerful dienophiles. The reaction below illustrates their utility in the preparation of dihydroanthraquinones (72). As an extension of this work, an

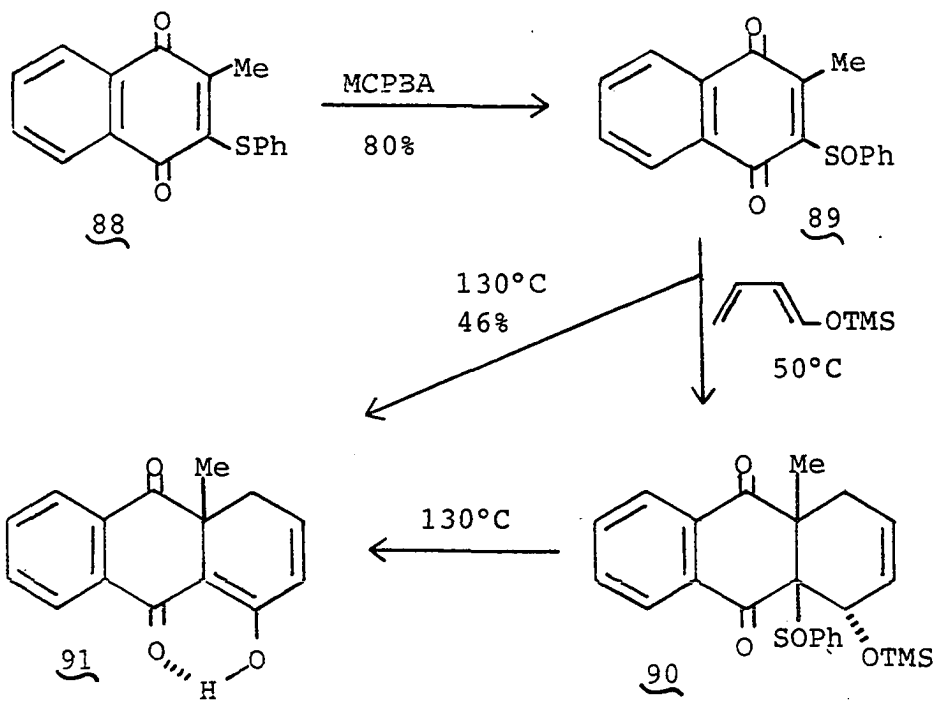


investigation of the Diels-Alder behavior of 2,3-disubstituted sulfinylnaphthoquinones was undertaken.

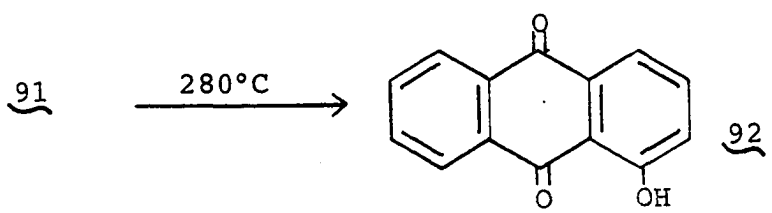
To produce a suitable system for this study, 2-methyl-3-phenylthionaphthoquinone 88 was prepared following a literature procedure (73). Oxidation with MCPBA afforded the sulfoxide 89 in 80% yield. Cycloaddition of 89 with 1-trimethylsilyloxy-1,3-butadiene was complete after only a few hours at 50°C. The extremely hygroscopic nature of the Diels-Alder adduct 90 made its isolation in pure form difficult. However, heating 90 at 130°C effected sulfoxide elimination and desilylation to afford the blocked anthraquinone 91! That 91 had been formed was based on its spectroscopic data. The 300 MHz ^{1}H NMR spectrum exhibited a sharp singlet at 15.6 ppm for the strongly hydrogen bound enol in addition to a sharp doublet of doublets (J = 10.2 and 4.2 Hz) at 6.28 ppm for the

olefinic proton adjacent to the enol. Apparently, desilylation was due to the benzenesulfenic acid coproduced in the sulfoxide elimination. In practice, all three chemical steps could be accomplished in one pot in 46% yield (Scheme V).

Scheme V

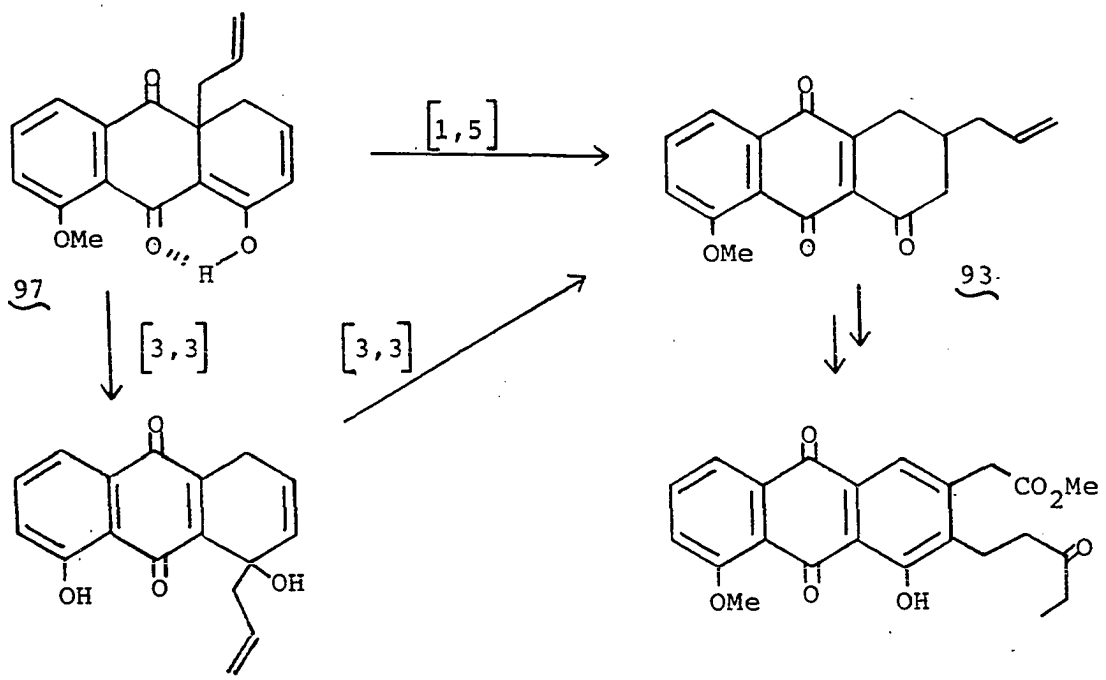


Heating 91 at 280°C for 30 minutes resulted in the extrusion of methane gas to provide 92. Literature precedent suggested that cleavage to a radical pair followed by hydrogen atom abstraction was the likely mechanism (74). The formation of anthraquinone 92 was confirmed by comparison with an authentic sample.

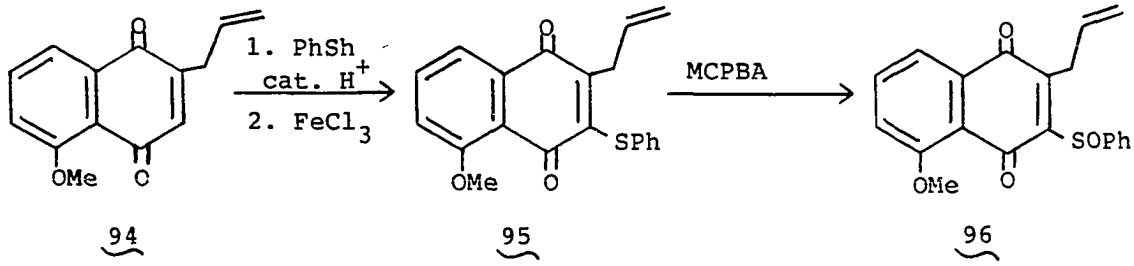


With these results, we desired to investigate the behavior of a corresponding allyl derivative of 89. In this system, alternate Woodword-Hoffman "allowed" pathways for rearrangement exist. Additionally, if rearrangement to a ketonaphthoquinone such as 93 occurred, a new approach toward aklavinone involving a Michael addition-intramolecular aldol condensation would be possible.

Scheme VI.



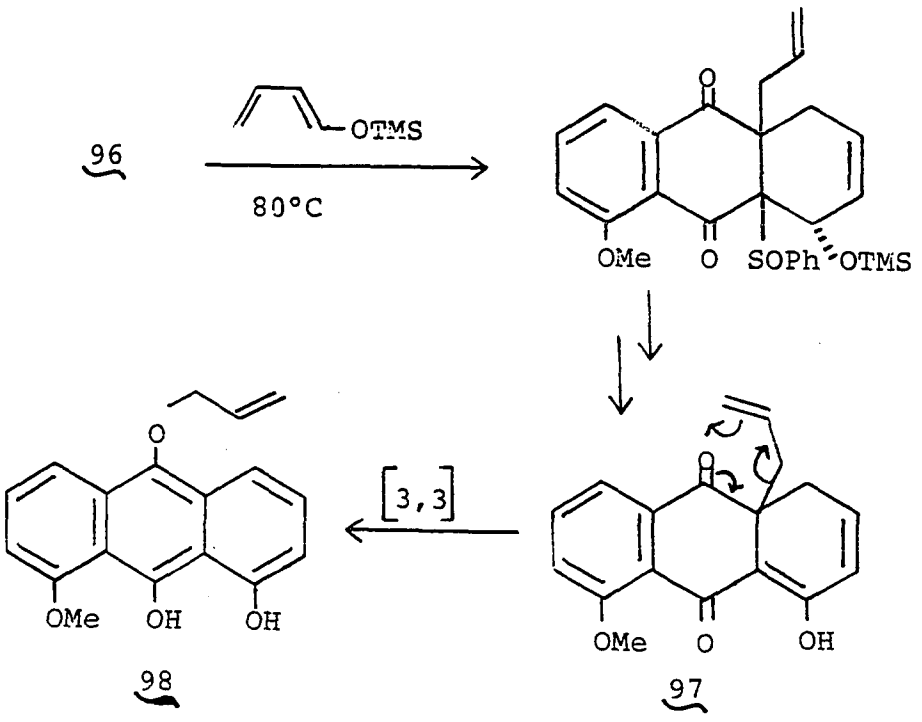
Toward this end, the known allyl-substituted naphthoquinone 94 (75) was prepared. Benzenethiol addition and oxidation proceeded smoothly to afford 96 in 85% overall

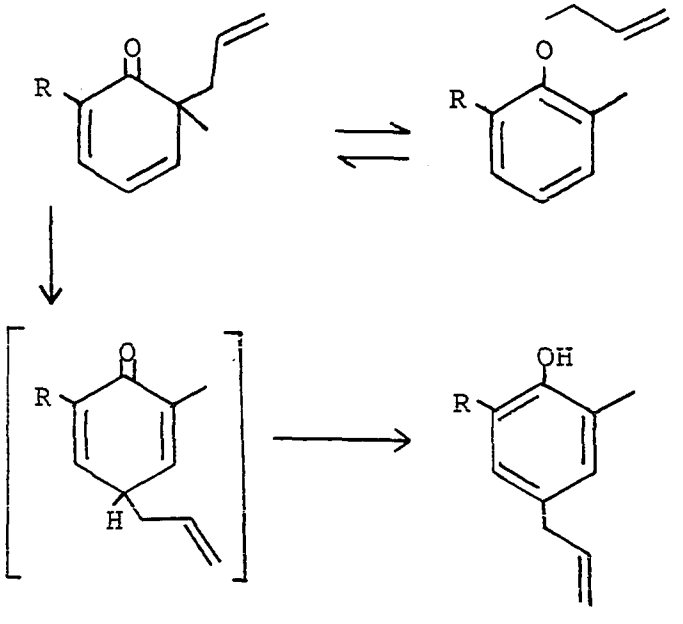


94 95 96

yield. Treatment of 96 with 1-trimethylsilyloxy-1,3-butadiene at ambient temperature resulted in a rapid reaction. Upon workup, however, a plethora of products were formed. Interestingly, conducting the Diels-Alder reaction at 80°C produced 98 as the only isolable product in 60% yield. Evidently, the desired sulfoxide elimination and desilylation steps had occurred followed by an apparent retro-Claisen rearrangement!

The reversibility of the allylphenyl ether Claisen rearrangement has been well established (76, 77). It is noteworthy that in "blocked aromatic" systems such as ours, rearrangement often continues to ultimately produce p-allylphenols (78, 79). Unfortunately, when 98 was heated


96
OTMS
80°C
OMe
O
SOPh
OTMS
[3,3]
OMe
OH
OH
98
OMe
O
OH
97


R
O
R
O
R
O
H
R
OH

R= H, CH_3

to temperatures sufficient to cause expulsion of methane gas from 91, only unreacted 98 and tarry materials were recovered. Evidently, the high barrier to disruption of aromaticity in the anthracene system precludes equilibration back to 97 and thence to 93.

EXPERIMENTAL

General

Unless otherwise noted, materials were obtained from commercial suppliers and were used without purification. THF and diethyl ether were distilled from sodium benzophenone ketyl under nitrogen prior to usage. Benzene was distilled from lithium aluminum hydride. Dichloromethane was distilled from calcium hydride. Unless otherwise noted, all reactions were conducted under an argon atmosphere. Unless otherwise noted, all organic extracts were dried over anhydrous sodium sulfate. Melting points were determined on a Fisher-Johns melting point apparatus and are uncorrected. Infrared spectra were obtained on a Beckman IR-4250 or a Perkin-Elmer model 1320 spectrophotometer. Nuclear magnetic resonance spectra were determined on a Varian EM-360 spectrometer. High field (300 MHz) proton spectra were obtained with a Nicolet Magnetics Corporation NMC-1280 spectrometer. All chemical shifts are reported in δ relative to tetramethylsilane as an internal standard. Coupling constants (J) are reported in Hz. Abbreviations: s = singlet, d = doublet, t = triplet, q = quartet, bs = broad singlet, m = multiplet, ABq, AB quartet. Carbon-13 NMR spectra were determined on a Nicolet NMC-1280 spectrometer and are reported in ppm relative to the central peak of $CDCl_3$ (77.06 ppm). High-resolution mass spectra were recorded on a Kratos model MS-50 spectrometer. Low-resolution

mass spectra were recorded on a Finnegan 4023 mass spectrometer. Silica gel used for flash chromatography (80) was 230-400 mesh (Kieselgel 60) purchased from EM Science. Gravity column chromatography was performed on 60-200 mesh silica gel purchased from Davison Chemical (WR Grace Inc.). Elemental analyses were performed by Galbraith Laboratories, Inc.

2-Phenylthio-1,4-naphthalenedione (43)

To a solution of sublimed naphthoquinone (8.19 g, 51.8 mmole) in 530 mL of absolute ethanol was added benzenethiol (5.43 mL, 53.0 mmole) and the brown solution stirred at ambient temperature for 16 h, whereupon a white precipitate had formed. The brown solution was treated with 30 g of iron(III)trichloride in 50 mL of water and stirred 2 h at ambient temperature. To this golden orange solution was added 200 mL of water and the yellow crystals which formed were filtered, washed with water, and dried in vacuo to provide 12.63 g (91%) of 43: mp 160-162°C (lit. (37) 159-161°C); 60 MHz ^{1}H NMR ($CDCl_3$) δ 6.12 (s, 1 H), 7.2-8.2 (m, 9 H); IR ($CDCl_3$) 3060, 1665, 1645, 1590, 1555, 1332, 1297, 1255, 1120, 855 cm^{-1}.

2-Cyano-1,4-dihydroxy-3-phenylthionaphthalene (44)

To a solution of sodium cyanide (7.0 g, 142.2 mmole) in 330 mL of 50% (V/V) aqueous ethanol at ambient temperature was

added 43 (12.63 g, 47.4 mmole) in 330 mL of dioxane and 85 mL of THF via an addition funnel dropwise. After the addition was complete, the reaction mixture was stirred 30 min at ambient temperature and then stood at 0° for 16 hours. The reaction mixture was then acidified with 100 mL of 1.5 N HCl and an additional 500 mL of water added. The resulting light brown precipitate was filtered and dried in vacuo to afford 11.78 g (84%) of 44 as a beige powder, yellow-gold needles from ethanol/water: mp 202-203°C with decomposition; 300 MHz ^{1}H NMR ($CDCl_3$, D_6 acetone) δ 7.10-7.30 (m, 5 H), 7.67 (m, 2 H), 8.35 (m, 2 H), 8.70 (s, 1 H), 10.35 (bs, 1 H); IR (mull) 3410, 3300-3100, 2210, 1570, 1450, 1370, 935, 770, 738 cm^{-1}; ^{13}C NMR 100.17, 107.36, 116.51, 124.26, 126.53, 127.68, 127.74, 128.24, 128.77, 129.68, 136.95, 150.83, 154.04 ppm; MS m/e 295, 294, 293, 215, 154, 136, 77; high resolution mass spectrum for $C_{17}H_{11}O_2SN$ requires 293.05105; determined 293.05099. Anal. Calcd for $C_{17}H_{11}O_2SN$: C, 69.61; H, 3.75. Found: C, 69.74; H, 3.84.

2-Cyano-3-phenylthio-1,4-naphthalenedione (45)

To a solution of 44 (2.93 g, 10.0 mmole) in 300 mL of 2:1 acetonitrile-THF was added slowly a solution of ceric ammonium nitrate (12.06 g, 22.0 mmole) in 50 mL of water. After stirring at ambient temperature for 30 min, the solvents were removed in vacuo and the residue dissolved in 300 mL of chloroform, washed with three 200 mL portions of water, dried

over magnesium sulfate, and filtered. The solvents were removed in vacuo and the residue crystallized from hexanes/ethyl acetate to provide 2.66 g (91%) of 45 as bright orange needles: mp 167-168°C; 300 MHz ^{1}H NMR ($CDCl_3$) δ 7.3-7.45 (m, 3 H), 7.48 (bd, 2 H), 7.65 (m, 2 H), 7.95 (m, 2 H); IR ($CDCl_3$) 2930, 2830, 2220, 1680, 1658, 1590, 1460, 1280, 1170, 820, 750, 710 cm^{-1}; ^{13}C NMR 110.06, 115.50, 119.73, 126.37, 126.98, 127.21, 129.54, 130.96, 131.07, 134.20, 134.94, 135.27, 160.88, 176.81, 179.75 ppm; MS, m/e 292, 291, 262, 235, 214, 182, 154, 126, 104, 76; high resolution mass spectrum for $C_{17}H_9O_2SN$ requires 291.03540, determined 291.03500; Anal. Calcd for $C_{17}H_9O_2SN$: C, 70.08; H, 3.09. Found: C, 69.88; H, 3.10.

(1α,4aβ,8aβ)-1-Acetoxy-8a-cyano-4a-phenylthio-1,4-dihydro-9,10-anthracenedione (46a)

A solution of 45 (290 mg, 1.0 mmole) and 1-acetoxy-1,3-butadiene (0.59 mL, 5.0 mmole) in 10 mL of benzene was placed in a thick-walled sealable tube and cooled to -78°C under a static argon atmosphere. The tube was then flame sealed and after warming to ambient temperature, was placed in an oil-bath at 130°C. After heating for 20 h at 130°C, the tube was cooled to -78°C and opened. The solvent and excess diene were removed in vacuo, and the residue was flash chromatographed on silica gel eluting with 3.5:1 hexanes/ethyl acetate to provide 30 mg of 45 and 249 mg (69%)

of 46a and 46b as a white solid, recrystallized from hexanes/ethyl acetate to provide 46a: mp 165-166°C; 300 MHz ^{1}H NMR ($CDCl_3$) δ 1.17 (s, 3 H), 2.65 (bd, 1 H, J = 18.6 Hz), 3.18 (dd, 1 H, J = 20.8 Hz and 5.1 Hz), 5.73 (d, 1 H, J = 4.8 Hz), 5.85 (m, 1 H), 6.15 (m, 1 H), 7.20-7.35 (m, 4 H), 7.41 (bt, 1 H, J = 7.2 Hz), 7.80 (m, 2 H), 8.05 (m, 2 H); IR (film) 3060, 2920, 2245, 1755, 1700, 1590, 1440, 1370, 1250, 1210, 1015 cm^{-1}; ^{13}C NMR 19.44, 30.54, 57.74, 59.10, 69.42, 114.18, 120.80, 126.97, 127.34, 129.25, 130.81, 131.90, 133.55, 133.62, 134.91, 135.70, 137.22, 167.63, 186.04, 186.58 ppm; MS m/e 403, 361, 294, 252, 250, 180, 151, 110; high resolution mass spectrum for $C_{23}H_{17}O_4SN$ requires 403.08784, determined 403.08750; Anal. Calcd for $C_{23}H_{17}O_4SN$: C, 68.47; H, 4.22. Found: C, 68.31; H, 4.53.

(1α,4aβ,8aβ)-8a-Cyano-4a-phenylthio-1-(trimethylsilyl)oxy-1,4-dihydro-9,10-anthracenedione (47)

To a suspension of 45 (7.50 g, 25.8 mmole) in 50 mL of benzene was added 1-(trimethylsilyl)oxy-1,3-butadiene (6.75 mL, 38.3 mmole) and the mixture was stirred at 40°C for 16 hours. The resulting light brown solution was concentrated in vacuo and the residue crystallized from diethyl ether/hexanes to afford 10.66 g (95.5%) of 47 as clear needles: mp 153.5-154.5°C; 300 MHz ^{1}H NMR ($CDCl_3$) δ -0.35 (s, 9 H), 2.60 (bd, 1 H, J = 18.6 Hz), 3.13 (ddd, 1 H, J = 18.6, 5.1, and 1.5 Hz), 4.68 (d, 1 H, J = 4.5 Hz), 5.76 (m, 1 H), 5.97 (m, 1 H),

7.15-7.30 (m, 4 H), 7.37 (m, 1 H), 7.21 (apparent dp, 2 H, J = 7.2 and 1.2 Hz), 7.90 (dd, 1 H, J = 7.5 and 1.5 Hz), 8.15 (dd, 1 H, J = 7.5 and 1.5 Hz); IR ($CDCl_3$) 3070, 3050, 2950, 1695, 1592, 1255, 1085, 845, 685 cm^{-1}; ^{13}C NMR -0.84, 30.61, 57.52, 60.92, 71.86, 115.17, 124.52, 126.42, 126.61, 127.72, 129.08, 129.14, 130.54, 133.00, 134.29, 134.36, 136.48, 137.17, 186.74, 188.19 ppm; MS m/e 433, 324, 282, 234, 197, 110; high resolution mass spectrum for $C_{24}H_{23}O_3SNSi$ requires 433.11680, determined 433.11697; Anal. Calcd: C, 66.49; H, 5.31. Found: C, 66.87; H, 5.42.

(4aβ,8aβ)-8a-Cyano-1-oxo-4a-phenylthio-4(2H)-9,10-anthracenedione (48)

To a solution of 47 (6.15 g, 14.2 mmole) in 200 mL of acetone at 0°C was added 16 mL of a 7 N Jones' reagent dropwise. The reaction was carefully monitored by TLC and after 30 min the reaction mixture was diluted with diethyl ether (100 mL) and quenched with 10 mL of 2-propanol. The salts were filtered and the filtrate was concentrated in vacuo. The residue was dissolved in 150 mL of diethyl ether and washed several times with 50 mL portions of brine and dried. The solvents were removed in vacuo and the residue crystallized from diethyl ether to afford 3.30 g (65%) of 48: mp 144-146°C; 300 MHz ^1H NMR ($CDCl_3$) δ 3.05 (dt, 1 H, J = 18.9 and 2.4 Hz), 3.34 (dd, 1 H, J = 18.9 and 6.3 Hz), 6.14 (dd, 1 H, J = 10.2 and 2.4 Hz), 7.22 (m, 1 H), 7.24-7.35 (m, 4 H),

7.45 (m, 1 H), 7.80 (m, 2 H), 8.02 (m, 1 H), 8.15 (m, 1 H); IR (CH_2Cl_2) 3060, 2215, 1710, 1685, 1585, 1370, 1250, 1205 cm^{-1}; ^{13}C NMR 32.07, 61.21, 66.19, 111.42, 126.06, 126.70, 128.02, 129.43, 131.23, 131.83, 132.26, 135.49, 137.40, 152,46, 182.31, 182.88, 186.58 ppm; MS m/e 359, 250, 222, 206, 166, 139, 110; high resolution mass spectrum for $C_{21}H_{13}O_3SN$ requires 359.06162, determined 359.06202; Anal. Calcd: C, 70.18; H, 3.62. Found: C, 70.27; H, 3.73.

2-Cyano-1-hydroxy-9,10-anthracenedione (53)

To a solution of 48 (113 mg, 0.314 mmole) in 6 mL of methylene chloride at 0°C was added meta-chloroperbenzoic acid (60 mg, 0.345 mmole) and the mixture stirred at 0°C for 5 hours. The solvent was removed in vacuo and the residue was suspended in diethyl-ether and stirred 5 hours. The solid remaining was filtered and dried to afford 72 mg (92%) of 53 as a light yellow sparingly soluble powder: mp > 250°C; 300 MHz ^1H NMR ($CDCl_3$) δ 7.57 (d, 1 H, J = 9 Hz), 7.90 (m, 2 H), 8.20 (m, 2 H), 8.29 (d, 1 H, J = 9 Hz); IR (mull) 3480, 3390, 2210, 1670, 1585, 1375, 1310, 1280 cm^{-1}; ^{13}C NMR 112.80, 120.33, 124.59, 125.17, 125.63, 126.33, 131.23, 131.38, 132.04, 132.78, 134.97, 165.61, 179.04, 179.72 ppm; MS m/e 249, 221, 193, 164, 138; high resolution mass spectrum for $C_{15}H_7O_3N$ requires 249.04260, determined 249.04264.

($1\alpha,8a\beta$)-1-Acetoxy-8a-cyano-1(2H)-9,10-anthracenedione (54)

To a solution of 46a (83 mg, 0.20 mmole) in 5 mL of methylene chloride at 0°C was added meta-chloroperbenzoic acid (35 mg, 0.20 mmole) and stirred at 0°C for 4 hours. The solution was concentrated in vacuo and the residue chromatographed on silica gel eluting with 4:1 hexanes/ethyl acetate to afford 6 mg of 46a and 41 mg (73%) of 64 as beige needles from hexanes/ethyl acetate: mp 146-149°C; 300 MHz ^{1}H NMR ($CDCl_3$) δ 1.85 (s, 3 H), 5.92 (dd, 1 H, J = 5.1 and 0.9 Hz), 6.65 (m, 2 H), 7.64 (dd, 1 H, J = 5.1 and 0.9 Hz), 7.84 (m, 2 H), 8.16 (d, 1 H, J = 7.5 Hz), 8.31 (d, 1 H, J = 7.8 Hz); IR (film) 3000, 2210, 1748, 1710, 1665, 1590, 1565, 1290, 1260, 1235, 1015, 860, 715 cm^{-1}; ^{13}C NMR 32.32, 59.62, 77.30, 126.11, 140.36, 140.49, 140.64, 141.88, 142.05, 142.35, 145.85, 146.88, 147.04, 148.24, 167.08, 180.78, 182.22 ppm; MS m/e 251, 234, 222, 178, 151, 130, 102; high resolution mass spectrum for $C_{17}H_{11}O_4N$ requires 293.06881, determined 293.06839.

($3\beta,4a\beta,8a\beta$)-3-Carboethoxymethyl)-8a-cyano-4a-phenylthio-1-(tert-butyldimethylsilyl)oxy-3,4-dihydro-9,10-anthracenedione (59)

To a solution of 48 (1.12 g, 3.12 mmole) in 18 mL of anhydrous acetonitrile was added 1-ethoxy-1-(tert-butyldimethylsilyl)oxyethylene (1.26 g, 6.24 mmole) at ambient temperature. The mixture was warmed to 40-45°C for 5 hours and then concentrated in vacuo. The residue was flash

chromatographed on silica gel eluting with 5:1 hexanes/ethyl acetate to afford 1.09 g (62%) of 59 as a white solid, colorless prisms from hexanes/ethyl acetate: mp 126-127°C; 300 MHz ^{1}H NMR ($CDCl_3$) δ -0.12 (s, 3 H), 0.20 (s, 3 H), 0.82 (s, 9 H), 1.26 (t, 3 H, J = 7.2 Hz), 1.88 (dd, 1 H, J = 13.7 Hz and 9.9 Hz), 2.38 (dd, 1 H, J = 14.9 and 8.7 Hz), 2.46 (dd, 1 H, J = 15.0 Hz and 5.7 Hz), 2.62 (dd, 1 H, J = 13.7 Hz and 6.8 Hz), 2.85 (m, 1 H), 4.15 (q, 2 H, J = 7.2 Hz), 4.96 (d, 1 H, J = 3.0 Hz), 7.28 (m, 5 H), 7.40 (m, 1 H), 7.80 (m, 2 H), 7.94 (m, 1 H), 8.11 (m, 1 H); IR (film) 3060, 2960, 2935, 2845, 1735, 1715, 1680, 1592, 1460, 1255, 840, 775 cm^{-1}; ^{13}C NMR 17.81, 29.76, 60.11, 60.54, 61.70, 95.99, 109.67, 115.04, 126.79, 128.87, 130.56, 131.12, 131.64, 137.70, 144.96, 170.95, 185.37, 186.13 ppm; MS m/e 504, 452, 416, 295; high resolution mass spectrum for $C_{31}H_{35}O_5SNSi$ requires 546.17706, determined 546.17690; Anal. Calcd: C, 68.11; H, 6.41. Found: C, 68.28; H, 6.49.

(3β,4aβ,8aβ)-3-Carboethoxymethyl-8a-cyano-4a-phenylsulfinyl-1-(tert-butyldimethylsilyl)oxy-3,4-dihydro-9,10-anthracenedione (61)

To a solution of meta-chloroperbenzoic acid (73 mg, 0.423 mmole) in 8 mL of methylene chloride at 0°C was added a solution of 59 (216 mg, 0.385 mmole) in 2 mL of methylene chloride dropwise. The reaction mixture was stood at 0°C 16 hours and concentrated in vacuo. The residue was chromatographed on silica gel eluting with 2:1 hexanes/ethyl

acetate to afford 213 mg (98%) of 61 as a 2.5:1 mixture of diastereomers. The major isomer was crystallized from hexanes/ethyl acetate as white needles: mp 185-187°C; 300 MHz ^{1}H NMR ($CDCl_3$) δ -0.11 (s, 3 H), 0.20 (s, 3 H), 0.83 (s, 9 H), 1.26 (t, 3 H, J = 7.2 Hz), 1.94 (dd, 1 H, J = 13.0 and 9.9 Hz), 2.40 (m, 3 H), 2.85 (m, 1 H), 4.14 (q, 2 H, J = 7.2 Hz), 4.93 (d, 1 H, J = 3.0 Hz), 7.28 (m, 2 H), 7.48 (m, 2 H), 7.59 (m, 1 H), 7.75 (m, 1 H), 7.86 (m, 2 H), 8.14 (dd, 1 H, J = 7.5 and 0.9 Hz); IR (film) 3060, 2920, 1710, 1670, 1655, 1590, 1255, 1205, 900, 830, 720 cm^{-1}; MS m/e 520, 452, 412, 396, 367, 339, 320, 295, 126, 110; high resolution mass spectrum for $C_{31}H_{35}O_6SNSi$ ($M^{+\cdot}-C_4H_9$) requires 520.12502, determined 520.12563.

(3β,8aβ)-3-Carbomethoxymethyl-8a-cyano-1-(tert-butyldimethylsilyl)oxy-3(2H)-9,10-anthracenedione (62)

A solution of 61 (820 mg, 1.45 mmole) in 40 mL of carbon tetrachloride was refluxed for 10 hours. The solvent was removed in vacuo and the residue was flash chromatographed on silica gel to provide 450 mg of 61 and 240 mg of 62 (83%) as a pale yellow oil which crystallized on standing at 0°C: mp 120.5-122°C; 300 MHz ^{1}H NMR ($CDCl_3$) δ 0.24 (s, 3 H), 0.30 (s, 3 H), 0.93 (s, 9 H), 2.49 (dd, 1 H, J = 15.9 and 6.6 Hz), 2.59 (dd, 1 H, J = 15.9 and 6.6 Hz), 3.59 (m, 1 H), 3.67 (s, 3 H), 5.09 (dd, 1 H, J = 3 and 0.9 Hz), 6.96 (m, 1 H), 7.75 (m, 2 H), 7.84 (m, 1 H), 8.14 (m, 1 H); IR (film) 3060, 2950, 2920,

2880, 2855, 2230, 1730, 1670, 1635, 1590, 1435, 1250, 1160, 1020, 840, 780, 650 cm^{-1}; ^{13}C NMR -4.90, -4.67, 18.08, 25.51, 33.91, 39.39, 51.76, 53.73, 105.62, 116.10, 127.44, 127.52, 129.76, 133.86, 134.02, 134.91, 139.26, 141.54, 170.72, 183.02, 185.24 ppm; MS m/e 437, 422, 380, 353, 320, 294, 264; high resolution mass spectrum for $C_{24}H_{27}O_5NSi$ requires 437.16586, determined 437.16551.

3-(Carbomethoxymethyl)-1-hydroxy-9,10-anthracenedione (64)

To a solution of 62 (160 mg, 0.366 mmole) in 10 mL of benzene at ambient temperature was added triethylamine (0.11 mL, 0.73 mmole) and the mixture was stirred at ambient temperature for 10 hours. The benzene was removed on a rotary evaporator and the residue dissolved in 20 mL of THF and 2 mL of 2 N HCl added. The mixture was stirred at ambient temperature for 16 hours, and poured into 50 mL of water. The aqueous phase was extracted with three 20 mL portions of methylene chloride, the organic extracts combined, and dried over magnesium sulfate. The solvents were removed in vacuo and the residue filtered under pressure through a plug of silica gel eluting with 5:1:1 hexanes/ethyl acetate/methylene chloride to provide 92 mg (85%) of 64 as a yellow solid, bright yellow needles from hexanes/diethyl ether: mp 147-148°C (lit. (62) 147°C); 300 MHz ^1H NMR ($CDCl_3$) δ 3.74 (s, 2 H), 3.76 (s, 3 H), 7.21 (d, 1 H, J = 1.5 Hz), 7.70 (d, 1 H, J = 1.5 Hz), 7.79 (m, 2 H), 8.25 (m, 2 H), 12.90 (s, 1 H); IR

(film) 3700-3200, 3058, 2960, 2920, 2850, 1720, 1670, 1635, 1580, 1475, 1435, 1350, 1225, 1140, 835, 810, 785 cm^{-1}; ^{13}C NMR 41.32, 52.38, 115.11, 120.65, 124.64, 126.81, 127.36, 129.12, 129.50, 133.46, 134.14, 134.56, 143.62, 162.64, 170.23, 182.04, 188.10 ppm; MS m/e 296, 253, 237, 209, 181, 152, 105; high resolution mass spectrum for $C_{17}H_{12}O_5$ requires 296.06848, determined 296.06831.

5-Acetoxy-2-phenylthio-1,4-naphthoquinone (69)

To a solution of juglone acetate (1.80 g, 8.33 mmole) in 60 mL of absolute ethanol at ambient temperature was added benzenethiol (0.43 mL, 4.17 mmole) in 13 mL of ethanol. After stirring at ambient temperature for 30 min, the reaction mixture was refluxed for 90 min and cooled to ambient temperature. After standing 48 hours long needles of 69 were formed. The mixture was filtered and the crystals washed with cold 50% ethanol to afford 960 mg (78%) of 69, orange-brown needles from ethanol: mp 186-188°C; 300 MHz ^1H NMR ($CDCl_3$) δ 5.97 (s, 1 H), 7.36 (d, 1 H, J = 7.8 Hz), 7.51 (m, 5 H), 7.72 (t, 1 H, J = 7.8 Hz), 8.11 (d, 1 H, J = 7.8 Hz); IR (CH_2Cl_2) 3050, 1770, 1668, 1645, 1190, 1100, 850 cm^{-1}; MS m/e 324, 282, 254, 237, 173, 120; high resolution mass spectrum for $C_{18}H_{12}O_4S$ requires 324.04564, determined 324.04577.

5-Hydroxy-2-phenylthio-1,4-naphthoquinone (70)

To a suspension of 69 (940 mg, 2.90 mmole) in 112 mL of absolute ethanol at ambient temperature was added 47 mL of concentrated hydrochloric acid (HCl). The suspension was refluxed for 15 min whereupon dissolution occurred. The reaction mixture was cooled and the resulting precipitate of 70 filtered. The filtrate was concentrated in vacuo and the precipitate and filtrate were dissolved in methylene chloride. The organic phase was washed with 200 mL of water, and the aqueous phase reextracted with two 100 mL portions of methylene chloride. The organic extracts were combined, washed with water, dried over magnesium sulfate, and filtered. The solvents were removed in vacuo to provide 813 mg (99%) of 70 as a light yellow powder, orange needles from diethyl ether: mp 140-142°C with decomposition; 300 MHz ^{1}H NMR ($CDCl_3$) δ 6.14 (s, 1 H), 7.34 (d, 1 H, J = 7.5 Hz), 7.64 (m, H), 7.75 (d, 1 H, J = 7.5 Hz), 12.16 (s, 1 H); IR ($CHCl_3$) 3500-2700, 3055, 1665, 1630, 1598, 1560, 1450, 1350, 1245, 1220, 850, 705, 690 cm^{-1}.

5-Methoxy-2-phenylthio-1,4-naphthoquinone (71)

To a solution of 70 (790 mg, 2.80 mmole) in 31 mL of chloroform was added silver(I) oxide (2.60 g, 11.2 mmole) and methyl iodide (1.80 mL, 28.0 mmole) and the reaction mixture allowed to stir at ambient temperature in the dark for 16 hours. The suspension was filtered through Celite and

concentrated in vacuo. Flash chromatography on silica gel eluting with 2:1 hexanes/ethyl acetate afforded 750 mg (90%) of 71 as a yellow solid, yellow needles from diethyl ether: mp 101-103°C; 300 MHz ^{1}H NMR ($CDCl_3$) δ 3.96 (s, 3 H), 6.02 (s, 1 H), 7.30 (d, 1 H, J = 8.4 Hz), 7.45-7.60 (m, 5 H), 7.63 (t, 1 H, J = 8.4 Hz), 7.78 (dd, 1 H, J = 7.8 and 1.0 Hz); IR (film) 3040, 1662, 1640, 1590, 1465, 1275, 1230, 840 cm^{-1}; ^{13}C NMR 56.55, 118.70, 119.71, 127.56, 130.25, 130.34, 130.55, 133.96, 134.34, 135.69, 153.17, 159.35, 181.56, 182.03 ppm; MS m/e 296, 237, 221, 187, 159, 110; high resolution mass spectrum for $C_{17}H_{12}O_3S$ requires 296.05072, determined 296.05041.

3-Cyano-5-methoxy-2-phenylthio-1,4-naphthoquinone (72)

To a solution of sodium cyanide (435 mg, 8.8 mmole) in 40 mL of 50% (V/V) ethanol was added 71 (740 mg, 2.50 mmole) in 20 mL of 3:1 dioxane/THF dropwise. After the addition was complete, the reaction mixture was stirred vigorously for 30 min. The reaction mixture was treated with 15 mL of 2 N HCl and poured into 60 mL of water. The aqueous solution was extracted twice with 15 mL portions of methylene chloride, the organic extracts dried, filtered, and concentrated in vacuo to yield an orange-brown solid. This solid was dissolved in 40 mL of 7:5 acetonitrile/THF and treated with ceric ammonium nitrate (3.4 g, 6.20 mmole) in 12 mL of water. After stirring 6 min at ambient temperature, the solution was diluted with 30

mL of methylene chloride and poured into 150 mL of water. The layers were separated and the aqueous phase was extracted with 60 mL of methylene chloride. The organic extracts were combined, washed with water, dried ($MgSO_4$), and filtered. The filtrate was concentrated in vacuo and the residue crystallized from ethyl acetate to provide 720 mg (90%) of 72 as violet needles: mp 227-229°C; 300 MHz ^1H NMR ($CDCl_3$) δ 4.00 (s, 3 H), 7.36 (m, 1 H), 7.49 (m, 3 H), 7.60 (m, 2 H), 7.75 (m, 2 H); IR (CH_2Cl_2) 2980, 1660, 1650, 1588, 1470, 1310, 1235, 1200, 840, 780 cm^{-1}; ^{13}C NMR 54.96, 109.17, 113.32, 117.60, 117.70, 128.24, 128.96, 133.29, 134.75, 165.28, 176.39, 182.53 ppm; MS m/e 321, 292, 236, 212, 166, 134, 76; high resolution mass spectrum for $C_{18}H_{11}O_3SN$ requires 321.04597, determined 321.04584; Anal. Calcd: C, 67.28; H, 3.42. Found: C, 67.48; H, 3.27.

(1α,4aβ,8aβ)-8a-Cyano-8-methoxy-4a-phenylthio-1-(trimethylsilyl)oxy-1,4-dihydro-9,10-anthracenedione (73)

Following the same procedure as that used to prepare 47, 72 (587 mg, 1.83 mmole) and 1-trimethylsilyloxy-1,3-butadiene (1.35 mL, 7.3 mmole) produced 745 mg (88%) of 73 as an off-white foamy solid: 300 MHz ^1H NMR ($CDCl_3$) δ -0.31 (s, 9 H), 2.55 (m, 1 H, collapses to a dt on irradiation of olefinic proton at δ 4.65), 2.98 (dd, 0.5 H, J = 5.1 and 1.6 Hz), 3.04 (dd, 0.5 H, J = 5.1 and 1.6 Hz), 4.01 (s, 3 H), 4.65 (d, 1 H, J = 4.8 Hz), 5.75 (m, 1 H), 5.93 (ddd, 1 H, J = 16, 7.5, and

2.4 Hz), 7.26 (m, 5 H), 7.38 (m, 1 H), 7.62 (dd, 1 H, J = 8.1 and 1.5 Hz), 7.67 (d, 1 H, J = 8.1 Hz); IR (film) 3020, 2950, 1680, 1580, 1290, 1220, 840 cm^{-1}; MS m/e 394, 354, 326, 264, 142; high resolution mass spectrum for $C_{25}H_{25}O_4SSiN$ requires 463.12737; determined 463.12695.

(4aβ,8aβ)-8a-Cyano-8-methoxy-1-oxo-4a-phenylthio-4(2H)-9,10-anthracenedione (74)

Following the same procedure as that used to prepare 48, oxidation of 73 (425 mg, 0.92 mmole) produced 300 mg (84%) of 74 as white prisms from diethyl ether: mp > 200°C with decomposition; 300 MHz ^1H NMR ($CDCl_3$) δ 2.97 (dt, 1 H, J = 19, 2.5, and 2.5 Hz), 3.23 (ddd, 1 H, J = 19, 6.1, and 0.9 Hz), 4.01 (s, 3 H), 6.09 (ddd, 1 H, J = 10.2, 2.7, and 0.9 Hz), 7.17 (m, 1 H), 7.30 (m, 5 H), 7.45 (m, 1 H), 7.62 (dd, 1 H, J = 8.1 and 0.9 Hz), 7.68 (d, 1 H, J = 8.1 Hz); IR ($CDCl_3$) 3010, 1710, 1690, 1585, 1290 cm^{-1}; ^{13}C NMR 32.11, 56.82, 60.92, 111.48, 119.01, 120.12, 120.50, 126.17, 126.85, 128.77, 129.34, 131.05, 133.36, 135.98, 137.53, 152.11, 159.92, 180.72, 183.31, 186.48 ppm; MS m/e 389, 280, 252, 224, 110; high resolution mass spectrum for $C_{22}H_{15}O_4SN$ requires 389.07219; determined 389.07182.

(3β,4aβ,8aβ)-3-Carbomethoxymethyl-8a-cyano-8-methoxy-4a-phenylthio-1-(tert-butyldimethylsilyl)oxy-3,4-dihydro-9,10-anthracenedione (75)

To a solution of 74 (200 mg, 0.514 mmole) in 3 mL of acetonitrile at ambient temperature was added 1-methoxy-1-

tert-butyldimethylsilyloxyethylene (215 mg, 1.13 mmole) in 0.5 mL of acetonitrile. The reaction mixture was placed in an oil bath at 45°C and stirred 16 hours. After this time, the reaction mixture was concentrated in vacuo and the residue flash chromatographed on silica gel using 5:1 hexanes/ethyl acetate as eluant to provide 222 mg (74%) of 75 as a white solid: mp 153-155°C; 300 MHz ^{1}H NMR ($CDCl_3$) δ -0.05 (s, 3 H), 0.18 (s, 3 H), 0.82 (s, 9 H), 1.85 (dd, 1 H, J = 13.5 and 9.9 Hz), 2.30 (dd, 1 H, J = 11.0 and 8.4 Hz), 2.44 (dd, 1 H, J = 11.0 and 8.4 Hz), 2.50 (dd, J = 13.5 and 6.7 Hz), 2.71 (m, 1 H), 3.66 (s, 3 H), 3.91 (s, 3 H), 4.89 (d, 1 H, J = 3.0 Hz), 7.24-7.34 (m, 5 H), 7.4 (m, 1 H), 7.68 (m, 2 H); IR (CH_2Cl_2) 2970, 1730, 1710, 1685, 1240 cm^{-1}; MS m/e 520, 468, 404, 311, 275; high resolution mass spectrum for $C_{30}H_{32}O_6SiSN$ requires 502.17197 ($M^{+\cdot}$-Me), determined 502.1722.

(3β,4aβ,8aβ)-3-Carbomethoxymethyl-8a-cyano-8-methoxy-4a-phenylsulfinyl-1-(tert-butyldimethylsilyl)oxy-3,4-dihydro-9,10-anthracenedione (76)

To a solution of 75 (95 mg, 0.165 mmole) in 5 mL of methylene chloride at 0° was added meta-chloroperbenzoic acid (38 mg, 0.181 mmole). The solution was stirred at 0°-5°C for 16 hours and the solvents were removed in vacuo to provide a beige solid. The solid was filtered through a short plug of silica gel with 1:1 hexanes/ethyl acetate to afford 95 mg (97%) of 76 as a 2.5:1 mixture of diastereomers which were

used in the next step without separation: IR (film) 2960, 1730, 1710, 1670, 1435, 1260, 1205, 1075, 1045 cm^{-1}.

3-(Carbomethoxymethyl)-1-hydroxy-8-methoxy-9,10-anthracenedione (78)

A suspension of the residue in 15 mL of carbon tetrachloride was heated at reflux for 16 hours. The solvent was removed in vacuo and the yellow residue passed through a short column of silica gel under pressure eluting with 2:1:1 hexanes/ethyl acetate/methylene chloride. The solvents were removed to afford a light yellow oil which was dissolved in 10 mL of benzene. To a benzene solution was added triethylamine (52 μL) and the solution stirred at ambient temperature for 3 hours. The solvent was removed in vacuo and the residue taken up in 6 mL of THF. To the THF solution was added 3 mL of a 2 N HCl and 0.6 mL of methanol and the whole stirred at ambient temperature for 15 hours. The majority of the solvents were removed in vacuo and the residue was dissolved in 30 mL of chloroform and transferred to a separatory funnel. The organic phase was washed twice with water and dried over magnesium sulfate. Flash chromatography on silica gel eluting with 2.5:1:1 hexanes/ethyl acetate/chloroform afforded 28 mg (52% overall yield from 76) of 78 as a yellow solid, yellow needles from methylene chloride/hexanes: sublimes at 165°C; 300 MHz ^1H NMR ($CDCl_3$) δ 3.72 (s, 2 H), 3.73 (s, 3 H), 4.08 (s, 3 H), 7.22 (d, 1 H, J = 1.5 Hz), 7.37 (d, 1 H, J = 8.4

Hz), 7.68 (d, 1 H, J = 1.5 Hz), 7.76 (t, 1 H, J = 8.4 Hz), 7.96 (d, 1 H, J = 8.4 Hz), 12.92 (s, 1 H); IR ($CDCl_3$) 3680, 1635, 1470, 1380, 1095 cm^{-1}; MS m/e 326, 280, 249, 221; high resolution mass spectrum for $C_{18}H_{14}O_6$ requires 326.07904, determined 326.0787.

5-Methoxy-3-phenylthio-1,4-naphthoquinone (80)

To a solution of 79 (540 mg, 1.91 mmole) in 25 mL of chloroform was added silver(I) oxide (1.76 g, 7.6 mmole) and methyl iodide (1.19 mL, 19.1 mmole) and the mixture stirred at ambient temperature in the dark for 24 hours. The reaction mixture was filtered through Celite and concentrated in vacuo to leave a yellow solid which was flash chromatographed on silica gel eluting with 2:1 hexanes/ethyl acetate to afford 462 mg (82%) of 80 as a light yellow solid, yellow needles from methylene chloride/hexanes: mp 185-188°C; 300 MHz ^1H NMR ($CDCl_3$) δ 4.02 (s, 3 H), 6.03 (s, 1 H), 7.26 (m, 1 H), 7.45-7.60 (m, 5 H), 7.65 (m, 2 H); IR ($CDCl_3$) 3060, 3010, 2940, 2840, 1665, 1658, 1585, 1290, 1270, 830 cm^{-1}.

(1α,4aβ,8aβ)-8-Methoxy-1-(trimethylsilyl)oxy-8a-thiophenyl-1,4-dihydro-9,10-anthracenedione (81)

To a solution of 80 (49 mg, 0.165 mmole) in 8 mL of toluene was added 1-trimethylsilyloxy-1,3-butadiene (0.15 mL, 0.825 mmole) and the reaction mixture heated at reflux for 56 hours. The reaction product was concentrated in vacuo and rapidly flash chromatographed on silica gel to provide 54 mg

(74%) of 81 as an unstable pale yellow oil: 300 MHz ^{1}H NMR ($CDCl_3$) δ -0.26 (s, 9 H), 2.45 (m, 1 H), 3.09 (m, 1 H), 3.97 (s, 3 H), 4.27 (d, 1 H, J = 5.0 Hz), 5.78 (m, 1 H), 5.98 (m, 1 H), 7.15-7.30 (m, 6 H), 7.45-7.65 (m, 2 H).

(4aβ,8aβ)-8-Methoxy-1-oxo-8a-thiophenyl-4(2H)-9,10-anthracenedione (82)

To a solution of 81 (30 mg, 0.068 mmole) in 5 mL of acetone was added Jones' reagent (8 drops of a 7 N solution) at 0°C. The reaction mixture was stirred 8 minutes at 0° and treated with 0.5 mL of isopropanol and 20 mL of diethyl ether and filtered through Celite. The filtrate was concentrated in vacuo below 30°C to afford 82 as a yellow unstable oil: 300 MHz ^{1}H NMR ($CDCl_3$) δ 2.92 (m, 2 H), 3.52 (t, 1 H, J = 6.3 Hz), 3.76 (s, 3 H), 6.14 (m, 1 H), 6.93 (apparent dt, 1 H, J = 9.9 and 4.2 Hz), 7.15-7.40 (m, 4 H), 7.45-7.55 (m, 2 H), 7.60-7.70 (m, 2 H).

(1α,4aβ,8aβ)-8a-Acetyl-1-(trimethylsilyl)oxy-1,4-dihydro-9,10-anthracenedione (85)

To a suspension of 2-acetyl-1,4-naphthoquinone (600 mg, 3.0 mmole) in 15 mL of benzene at 10°C was added 1-trimethylsilyloxy-1,3-butadiene (1.03 mL, 5.9 mmole). The reaction mixture was slowly warmed to ambient temperature and stirred at ambient temperature for 16 hours. The reaction product was concentrated in vacuo and the residue filtered quickly through a short plug of silica gel to afford 970 mg (94%) of 85

contaminated with approximately 8% of the "exo" Diels-Alder adduct, beige prisms from diethyl ether/hexanes: mp 158-160°C; 300 MHz ^{1}H NMR ($CDCl_3$) δ -0.32 (s, 9 H), 2.00 (dd, 1 H, J = 18.1 and 6.9 Hz), 2.40 (s, 3 H), 3.12 (dd, 1 H, J = 18.0 and 1.5 Hz), 3.87 (d, 1 H, J = 6.9 Hz), 4.80 (m, 1 H), 5.88 (m, 2 H), 7.60-7.80 (m, 2 H), 7.90-8.05 (m, 2 H); IR (film) 3060, 3025, 2950, 1720, 1705, 1670, 1595, 1250, 730 cm^{-1}.

(4aβ,8aβ)-8a-Acetyl-1-oxo-4(2H)-9,10-anthracenedione (86)

To a solution of 85 (166 mg, 0.48 mmole) in 10 mL of acetone at 0°C was added Jones' reagent (55 drops of a 7 N solution). After stirring 15 minutes at 0°C, the reaction mixture was treated with 1.0 mL of isopropanol and 30 mL of diethyl ether and filtered through Celite. The filtrate was concentrated in vacuo, diluted with 10 mL of 1:1 diethyl ether/methylene chloride and filtered through a plug of glass wool. The filtrate was evaporated to dryness to afford 92 mg (71%) of 86 as a beige powder: mp 130-132°C; 300 MHz ^{1}H NMR ($CDCl_3$) δ 2.38 (s, 3 H), 2.57 (m, 1 H), 3.27 (m, 1 H), 4.25 (t, 1 H, J = 2.0 Hz), 6.11 (bd, 1 H, J = 10.2 Hz), 7.09 (m, 1 H), 7.77 (m, 2 H), 8.05 (m, 2 H); IR (film) 1720, 1692, 1670, 1270, 1250, 730 cm^{-1}.

2-Methyl-3-phenylsulfinyl-1,4-naphthoquinone (89)

To a solution of 88 (5.0 g, 17.8 mmole) in 120 mL of methylene chloride at -5°C was added meta-chloroperbenzoic acid (3.74 g, 21.7 mmole) and the reaction mixture slowly warmed to ambient temperature. After stirring three hours at ambient temperature, the reaction mixture was cooled to 0°C and isobutylene gas passed in for 30 min. The reaction mixture was poured into 100 mL of water and carefully basified with saturated aqueous sodium bicarbonate solution. The layers were separated and the organic phase washed twice with 100 mL portions of water and dried. The drying agent was filtered and the filtrate concentrated to ca. 50 mL in vacuo. To the concentrated solution was added 200 mL of hexanes and the solution stood overnight. The resulting crystals were filtered to afford 4.16 g (79%) of 89: mp 126-129°C; 300 MHz ^{1}H NMR ($CDCl_3$) δ 2.52 (s, 3 H), 7.45-7.60 (m, 3 H), 7.72 (m, 2 H), 7.84 (m, 2 H), 8.01 (m, 2 H); IR ($CHCl_3$) 3005, 1665, 1280, 1045, 705 cm^{-1}; ^{13}C NMR 9.24, 124.69, 126.90, 126.66, 129.08, 130.67, 130.94, 131.41, 133.98, 134.06, 142.75, 147.95, 149.34, 181.89, 183.31 ppm; MS m/e 296, 280, 247, 172, 125; high resolution mass spectrum for $C_{17}H_{12}O_3S$ requires 296.05072; determined 296.05033.

1-Hydroxy-4a-methyl-4(2H)-9,10-anthracenedione (91)

In a dry 30 mL sealable tube was placed 89 (510 mg, 1.72 mmole), 1-trimethylsilyloxy-1,3-butadiene (0.75 mL, 4.3

mmole), and trimethylphosphite (0.40 mL, 3.45 mmole) and diluted with 10 mL of carbon tetrachloride. The solution was cooled to -78°C and sealed under high vacuum. The tube was placed in an oil bath at 60°C for 1 h, then heated at 130°C for 12 hours. The tube was cooled to -78°C, opened, and concentrated in vacuo. The light yellow semi-solid residue was flash chromatographed on silica gel eluting with 4:1 hexanes/ethyl acetate to afford 154 mg (46%) of 91 as a light yellow oil: 300 MHz ^{1}H NMR ($CDCl_3$) δ 1.36 (s, 3 H), 2.65 (apparent dt, 1 H, J = 19.2 and 2.4 Hz), 2.80 (dd, 1 H, J = 19.2 and 6.3 Hz), 6.28 (dd, 1 H, J = 10.2 and 2.7 Hz), 6.94 (m, 1 H), 7.65 (m, 1 H), 7.78 (m, 1 H), 8.06 (d, 1 H, J = 7.5 Hz), 8.12 (d, 1 H, J = 7.5 Hz), 15.58 (s, 1 H); IR (film) 3080, 2980, 2940, 1695, 1640, 1600, 1570, 1460, 1300, 1150, 910, 740 cm^{-1}; ^{13}C NMR 27.52, 32.69, 45.20, 109.76, 125.07, 127.01, 127.88, 132.10, 133.12, 134.23, 136.39, 145.84, 167.11, 186.76, 200.05 ppm; MS m/e 240, 225, 142, 125.

8-Methoxy-2-phenylthio-4-(2-propenyl)-1,4-naphthoquinone (95)

To a solution of 94 (1.00 g, 4.38 mmole) in 50 mL of methylene chloride at -20°C was added benzenethiol (0.90 mL, 8.76 mmole) followed by para-toluenesulfonic acid monohydrate (5 mg, 0.026 mmole). The reaction mixture was slowly warmed to ambient temperature and was stirred 3.5 h at ambient temperature. The reaction product was concentrated in vacuo, dissolved in 25 mL of acetonitrile, and treated with 70%

aqueous ferric trichloride (10 mL). After stirring 2 h at ambient temperature, the crude reaction product was poured into 100 mL of water, extracted twice with 50 mL portions of methylene chloride. The organic extracts were combined, washed with water, and dried over magnesium sulfate, and filtered. The solvents were removed in vacuo and the residue crystallized from hexanes/ethyl acetate to afford 1.35 g (93%) of 95 as red-orange needles: mp 112-113°C; 300 MHz ^{1}H NMR ($CDCl_3$) δ 3.65 (bd, 2 H, J = 6.3 Hz), 3.85 (s, 3 H), 5.05-5.25 (m, 2 H), 5.85 (m, 1 H), 7.15-7.30 (m, 4 H), 7.36 (m, 2 H), 7.62 (t, 1 H, J = 8.1 Hz), 7.73 (dd, 1 H, J = 8.1 and 0.9 Hz); IR ($CHCl_3$) 3005, 1662, 1650, 1590, 1275, 1240 cm^{-1}; ^{13}C NMR 33.19, 56.52, 117.34, 117.80, 119.30, 121.03, 127.14, 129.08, 130.62, 133.29, 134.39, 134.55, 147.75, 148.07, 159.59, 178.94, 182.47 ppm; MS m/e 336, 288, 259, 110; high resolution mass spectrum for $C_{20}H_{16}O_3S$ requires 336.08202; determined 336.08213.

8-Methoxy-2-phenylsulfinyl-4-(2-propenyl)-1,4-naphthoquinone (96)

Following the procedure for the preparation of 89, 95 (1.0 g, 2.97 mmole) afforded 0.99 g (94%) of 96 as a dark red oil: 300 MHz ^{1}H NMR ($CDCl_3$) δ 3.94 (s, 3 H), 3.90-4.15 (m, 2 H), 4.95-5.15 (m, 2 H), 5.80 (m, 1 H), 7.28 (dd, 1 H, J = 8.1 and 2.1 Hz), 7.35-7.55 (m, 3 H), 7.60-7.70 (m, 2 H), 7.87 (m, 2 H); ^{13}C NMR 26.29, 56.54, 118.10, 118.21, 118.69, 119.67,

125.29, 129.24, 130.75, 133.75, 133.80, 135.55, 143.49, 148.17, 150.38, 159.65, 181.85, 183.52 ppm.

1,10-Dihydroxy-9-methoxy-5-(2-propenyl)oxyanthracene (98)

A solution of 96 (100 mg, 0.284 mmole) and 1-trimethylsilyloxy-1,3-butadiene (0.20 mL, 1.13 mmole) in 10 mL of carbon tetrachloride was heated at reflux for 20 h. The reaction mixture was cooled, concentrated in vacuo, and the residue flash chromatographed on silica gel eluting with 2:1 hexanes/ethyl acetate to afford 51 mg (60%) of 98 as a light yellow oil, blue-green fluorescence in dilute solution: 300 MHz ^{1}H NMR ($CDCl_3$) δ 4.05 (s, 3 H), 4.78 (m, 2 H), 5.79 (m, 1 H), 6.84 (d, 1 H, J = 7.5 Hz), 7.24 (m, 1 H), 7.30-7.50 (m, 3 H), 7.65-7.80 (m, 3 H), 9.85 (s, 1 H); IR (film) 3500-3200, 3060, 2940, 2840, 1615, 1600, 1445, 1400, 1265, 1090, 1040, 910, 805, 690, 670 cm^{-1}; ^{13}C NMR 56.36, 64.96, 106.08, 114.14, 116.81, 118.53, 120.94, 121.34, 124.45, 127.99, 128.79, 129.61, 143.02, 145.16, 149.17, 156.59 ppm.

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68. A variety of Lewis acids including $TiCl_4$, $BF_3 \cdot OEt_2$, and TMSOTf were employed with similar results. On a small scale, the ketene acetal was used as the solvent, however only unreacted enone was obtained.

69. We thank Dr. Clayton Heathcock (University of California at Berkeley) for attempting this reaction with his high pressure apparatus.

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PART III: SYNTHETIC APPROACHES TO THE PYRANONAPHTHOQUINONE ANTIBIOTICS: TOTAL SYNTHESIS OF NANAOMYCIN A AND DEOXYFRENOLICIN

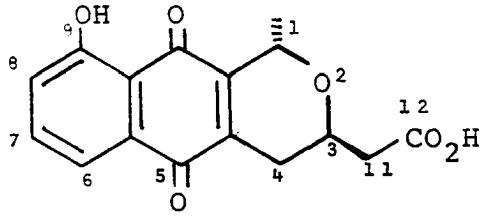
INTRODUCTION

Nanaomycin A and deoxyfrenolicin are members of the pyranonaphthoquinone class of antibiotics. Due to their useful biological activity and interesting structures, this class of antibiotics has received considerable attention from the synthetic viewpoint.

This manuscript will discuss the details of a synthetic program which resulted in a general synthesis of the moderately complex pyranonaphthoquinones nanaomycin A and deoxyfrenolicin.

HISTORICAL

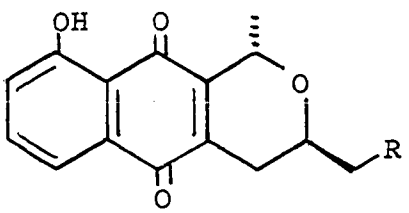
The pyranonaphthoquinone antibiotics are a growing class of compounds isolated from various species of Streptomyces. All contain the 2,3-fused pyran-naphthoquinone ring system in addition to alkyl and acetic acid residues. The general structure and numbering scheme for the pyranonaphthoquinone antibiotics is shown below.



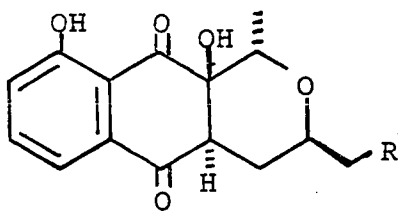
Although nearly all biologically active members of this class contain alkyl and acetic acid groups in a trans relationship on the pyran ring, a wide variety of additional functionality may also be present. Spiroketal, lactone, carbohydrate, and carbocyclic units are commonly appended to the basic structural unit shown above. For this reason, information pertaining to each subclass of antibiotics will be presented separately.

The nanaomycin (NNM) subclass is the largest of the pyranonaphthoquinone antibiotics. Nanaomycins A 1 and B 8 were isolated in 1974 from Streptomyces rosa variant notoensis strain OS-3966 (1). The two antibiotics were found to inhibit

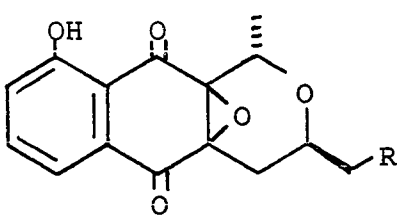
a variety of Gram-positive bacteria, mycoplasmas, and fungi at low concentrations. Additionally, the toxicities (LD_{50}) of the two new antibiotics were low in mice (1b). The structures of nanaomycins A and B as well as the other known nanaomycins are shown below.



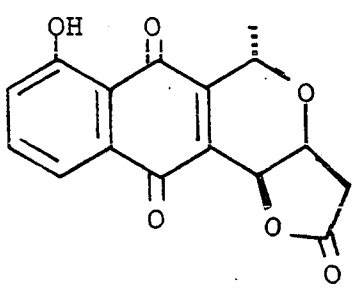
1: R = CO_2H, nanaomycin A
2: R = $CONH_2$, nanaomycin C
3: R = CO_2CH_3, nanaomycin αA
4: R = CH_2OH, nanaomycin βA



8: R = CO_2H, nanaomycin B
9: R = CO_2CH_3, nanaomycin αB



5: R = CO_2H, nanaomycin E
6: R = CO_2CH_3, nanaomycin αE
7: R = CH_2OH, nanaomycin βE



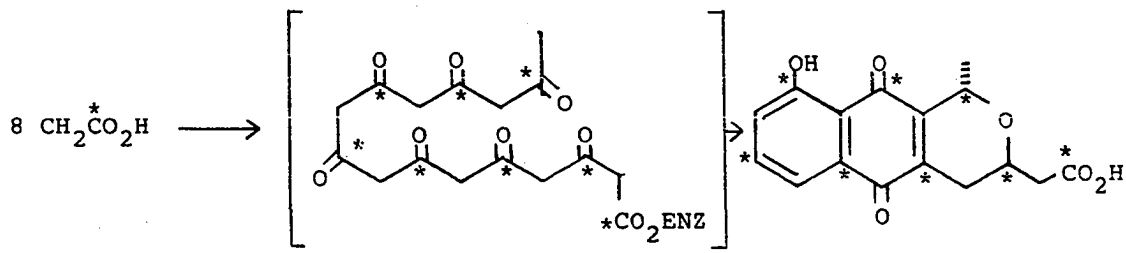
10: (-)-nanaomycin D
11: (+)-nanaomycin D = kalafungin

The probable biosynthetic pathway for nanaomycin was elucidated through the use of radiolabeled acetate (2). As in

other quinone containing antibiotics, the nanaomycins are synthesized from acetate *via* a polyketide intermediate (Scheme I).

The isolation and structure elucidation of nanaomycins C 2 (3), D 10 (4), and E 5 (5) soon followed. All three members were isolated from the same *Streptomyces* species as the nanaomycins A and B. Indeed, nanaomycins A-E have been shown to interconvert by either microbial or chemical transformations during their biosynthesis (6). Utilizing cerulenin, a specific inhibitor of fatty acid and polyketide biosynthesis, the pathway NNM-D → NNM-A → NNM-E → NNM-B was proposed (Scheme II). The formation of NNM-C was only observed when an excess amount of NNM-A was present in the culture medium, therefore, its participation in the bioconversion sequence is questionable.

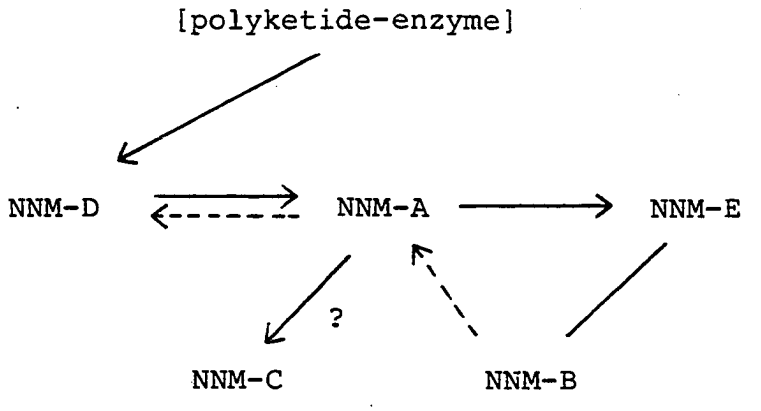
Scheme I.



* - denotes the position of a ^{13}C label

Due to the novel biochemical transformations implied in the above scheme, detailed studies relating to the mechanism

Scheme II.



⟵ : microbial transformation

⟵ : chemical transformation

of each transformation were warranted. Omura et al. demonstrated that the conversion of NNM-A to NNM-B is a two-step process, and confirmed NNM-E as the intermediate (figure 1) (7). Additionally, the first biosynthetic step in the nanaomycin interconversion was shown to involve reduction of NNM-D to a hydroquinone, cleavage to an enone intermediate, and tautomerization to produce NNM-A (Figure 2) (8).

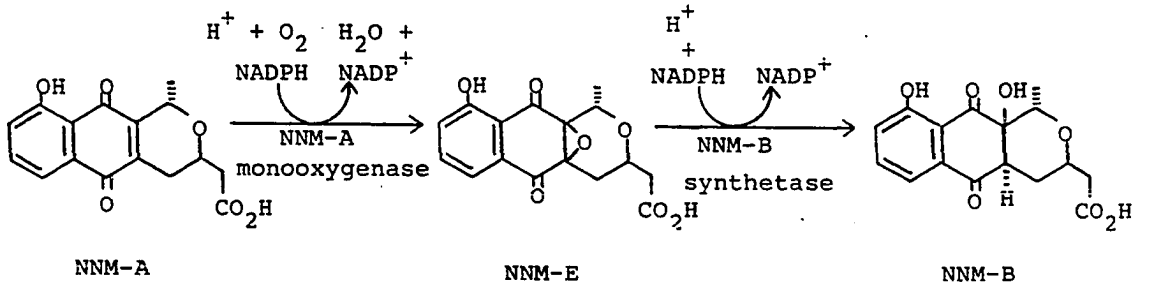


Figure 1. Bioconversion of NNM-A to NNM-B.

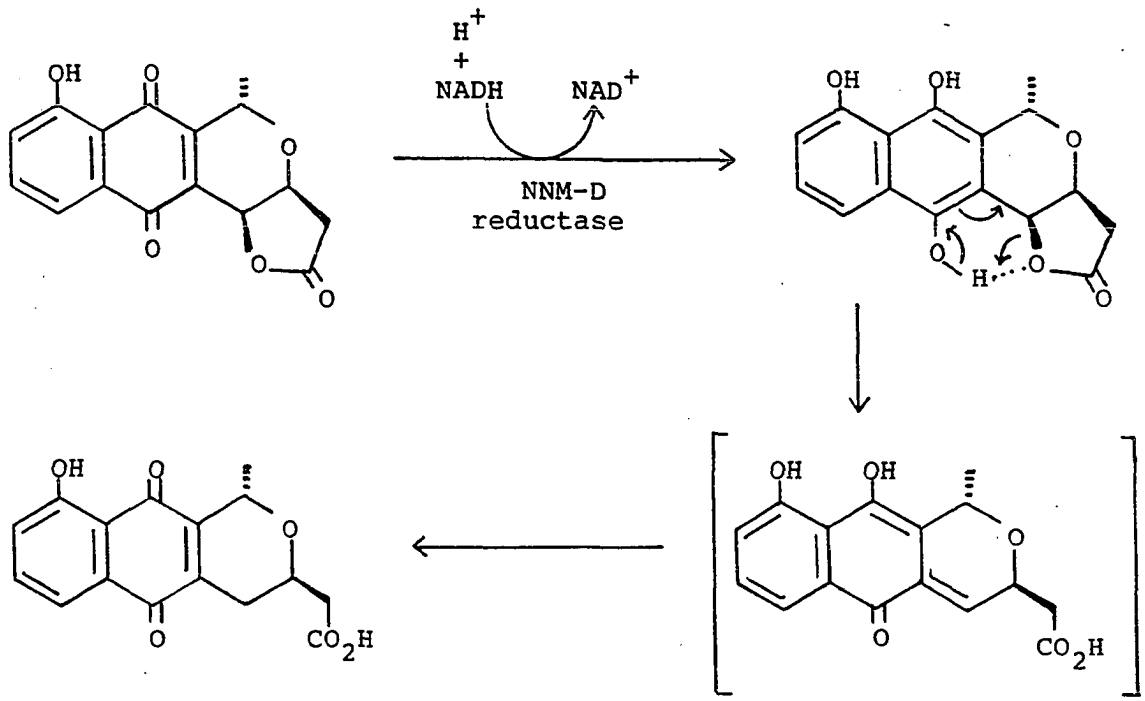
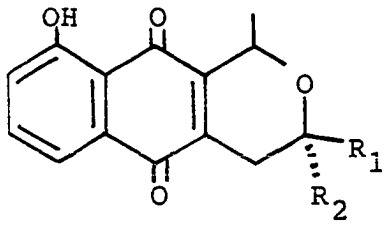


Figure 2. Bioconversion of NNM-D to NNM-A.

Kalafungin 11, the enantiomer of nanaomycin D, was isolated in 1968 by workers at the Upjohn Company from Streptomyces tanashiensis strain kala (UC-5063) (9). The absolute configuration of kalafungin was determined by comparison of its optical rotary dispersion curve with those of the known compounds elutherin 12a and isoelutherin 12b (10).

The isolation and biological properties of five other nanaomycin related antibiotics were reported in 1983. Nanaomycins αA 3, βA 4, αB 9, αE 6, and βE 7 were isolated from

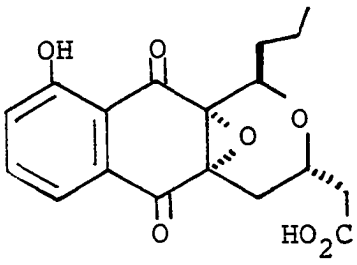


12a: $R_1 = CH_3$, $R_2 = H$
12b: $R_1 = H$, $R_2 = CH_3$

Streptomyces strain OM-173 (11). From this study and the findings of others (3, 9), it is clear that modification of the substituent at C-12 to anything other than an acid or lactone lowers the antimicrobial activity considerably. However, removal of oxygenation at C-9 does not seem to affect the activity at all (12). Interestingly, the C-9 acetate of nanaomycin A has strong anti-bacterial activity, while a similar methyl ether has extremely low activity (1).

A subclass of pyranonaphthoquinone antibiotics that are C-1 n-propyl analogs of the nanaomycins also exists. Frenolicin 13 (13, 14), deoxyfrenolicin 14 (14, 15), and frenolicin B 15 (15) have been isolated and their structures determined. The frenolicin subclass are similarly active against bacteria, pathogenic fungi, and mycoplasmas. However, they differ from the nanaomycins in absolute configuration at the C-1 and C-3 positions. Thus, the frenolicins have configurations 1R and 3R and the nanaomycins have configurations 1S and 3S. Notably, frenolicin B is

particularly effective against Eimeria tenella, a pathogenic fungus that causes serious problems in the poultry industry (16).



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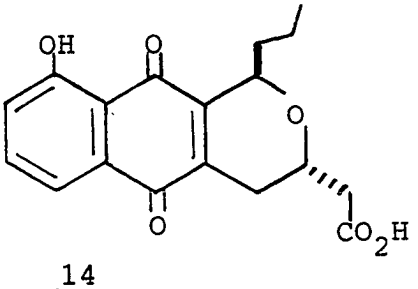

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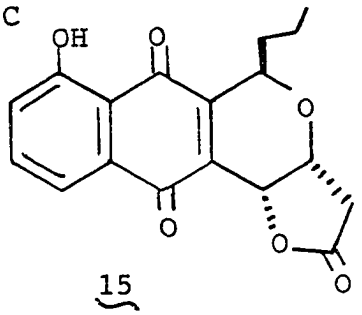

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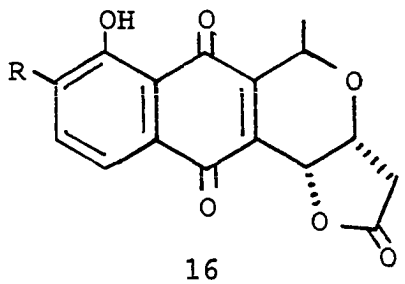
Lactoquinomycin 16 (17) and lactoquinomycin B 17 (18) are pyranonaphthoquinone antibiotics produced from Streptomyces tanashiensis strain IM8442T. Isolated in 1985 and 1986, these compounds are similar to the frenolicins in absolute configuration, but have a methyl group at C-1 as in the nanaomycin series. In addition to their good anti-bacterial activity, they are excellent cytotoxins, showing strong inhibitory activity in vitro against K562 human mycloid leukemia, L1210 and P388 murine leukemia, and L5178 murine lymphoblastoma in culture (19). High in vivo activity against Ehrlich ascites carcinoma in mice was also observed (18).



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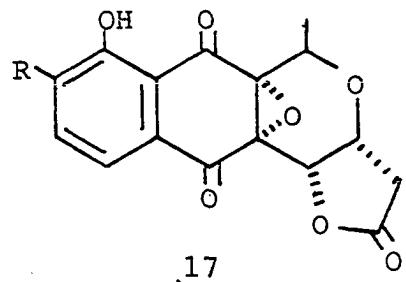

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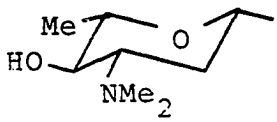
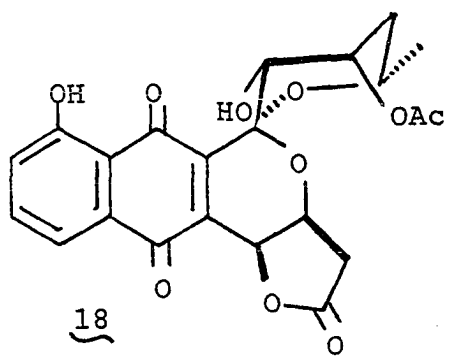


= R

More importantly, these compounds exhibit low acute toxicity in mice. Although additional testing is necessary, the lactoquinomycins appear promising as antitumor agents.

More complex members of the pyranonaphthoquinone family also exist. Griseusins A 18 and B 19 were isolated from Streptomyces griseusis strain K-63 by Tsuji and coworkers in 1975 (20). Their gross structures and absolute stereochemistry were later determined by spectroscopic comparison (21) with the known compound actinorhodinindazolquinone (22). However, by chemical synthesis the originally assigned absolute stereochemistry was found to be antipodal (23).

Granaticin 20 can be isolated from Streptomyces olivaceus or Streptomyces limogenes (24, 25). Its structure was determined by a variety of spectroscopic methods including x-ray crystallographic analysis (26) and is shown above. Granaticin is highly active against Gram-positive bacteria and



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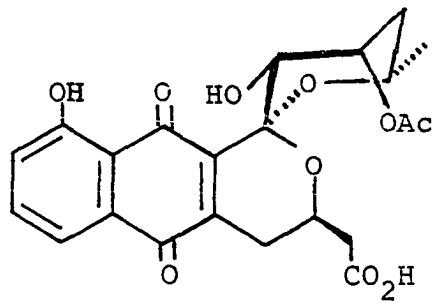

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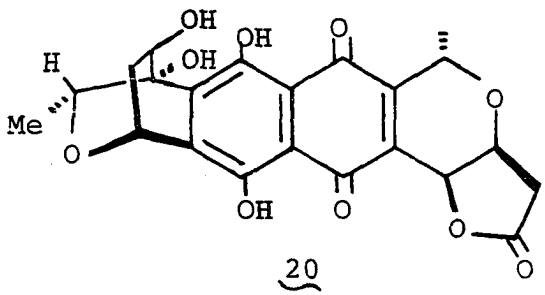
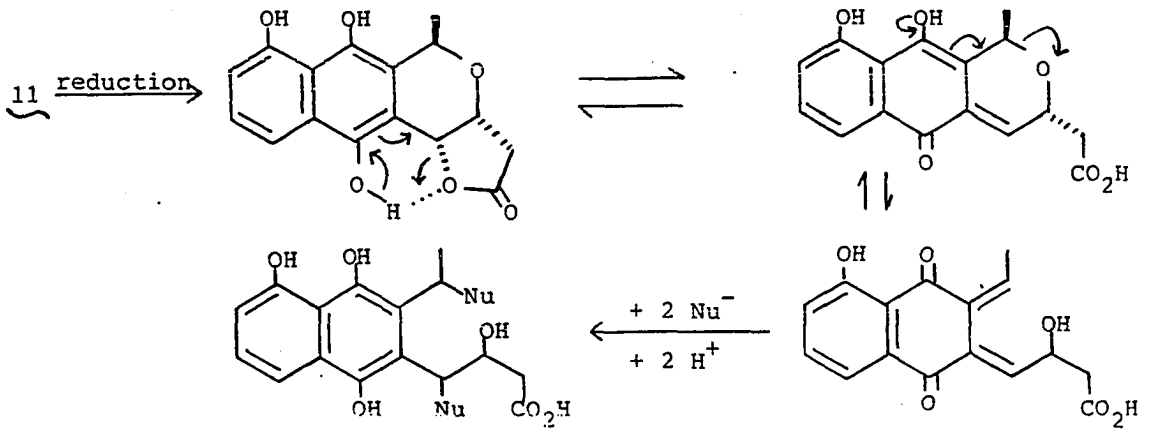


20

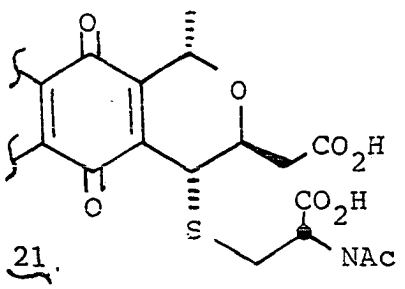
shows significant in vivo antitumor activity against P-388 lymphocytic leukemia in mice (25).

Although the actual mode of action for the pyranonaphthoquinone antibiotics is presently unknown, Moore has postulated a "bio-reductive alkylation mechanism" (27). The proposed mechanism is illustrated below with kalafungin (scheme III). Reduction, followed by equilibration to a quinone methide may occur. This is similar to the bioconversion of NNM-D to NNM-A (figure 2). Nucleophilic trapping of the quinone methide by an enzyme or another biological nucleophile is a possible pathway for antimicrobial activity. Another mechanism involving the formation of semiquinone radicals with

Scheme III.



subsequent production of the superoxide radical has been suggested (28). However, the recent isolation of a N-acetyleysteinyl conjugate 21 from granaticin producing strains of Streptomyces violaceoruber supports the "bio-reductive alkylation" mechanism (29).



21

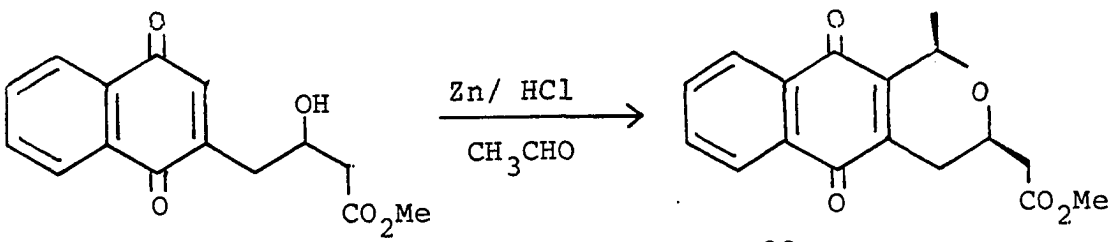
Due to their useful antimicrobial and antitumor properties, the pyranonaphthoquinones have received considerable attention from the synthetic standpoint. To date, total syntheses of the elutherins, the nanaomycins,

kalafungin, the frenolicins, and the griseusins have been reported. Although the elutherins do not show significant biological activity, their total synthesis has been of importance for the testing of general synthetic strategies, and for structural comparison with the more complex pyranonaphthoquinones. The total syntheses of the elutherins (30-33) will not be covered in this historical; the interested reader is encouraged to refer to the references provided for an entry into the literature.

The successful total syntheses of the pyranonaphthoquinones have involved a variety of interesting strategies. Formation of the naphthoquinone-pyran ring system has been accomplished by the following methods: reductive alkylation of a naphthoquinone, acid or base catalyzed etherification, organometallic processes, and addition of nucleophiles to activated naphthoquinones. However, in almost every case, poor stereoselectivity has been realized in the placement of the alkyl and acetic acid residues trans on the pyran ring. To solve this problem, isomerization of a cis isomer to the natural trans configuration has been employed. Fortunately, this is a favorable equilibrium and a preponderance of the natural isomer is easily obtained.

St. Pyrek and coworkers were the first to utilize reductive hydroxyalkylation in their synthesis of deoxynanaomycin methyl ester (34). In the key step, β-hydroxy

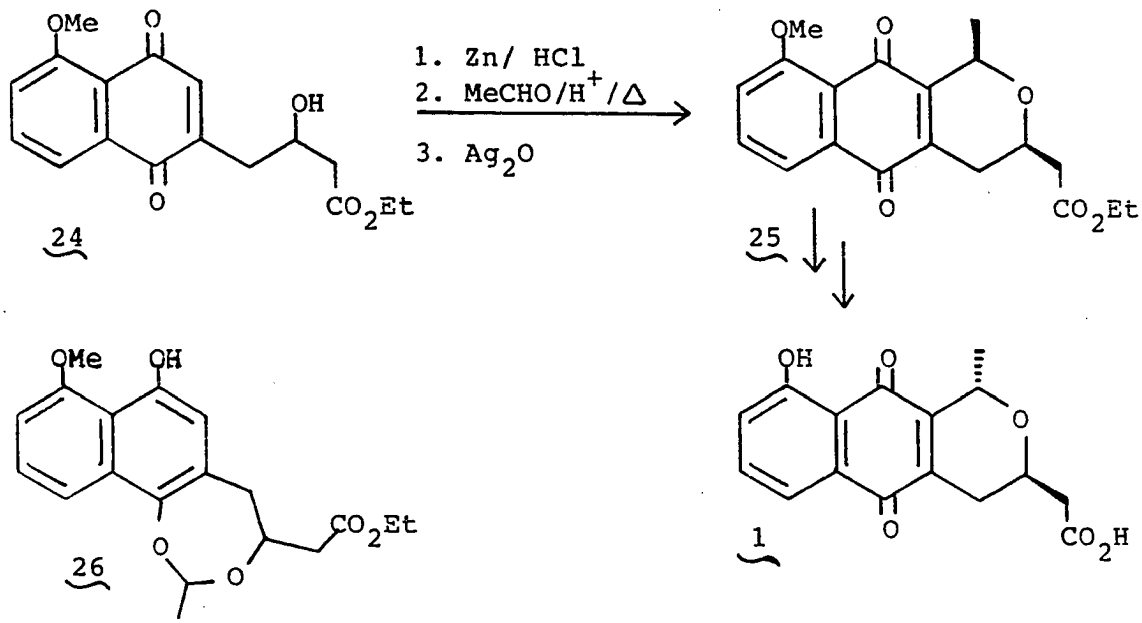
ester 22 was reduced and alkylated *in situ* with acetaldehyde. After aerial oxidation, the *cis*-pyran 23 was obtained in 15% yield.



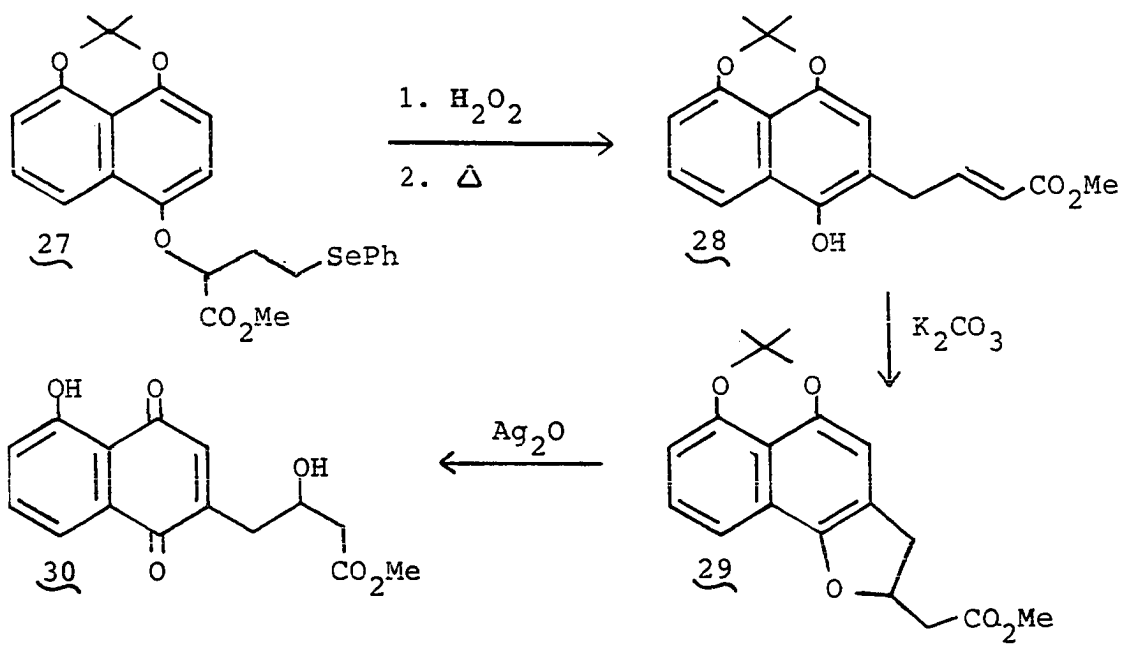
22 23

The probable mechanism of the reductive alkylation was established by Li and Ellison in their synthesis of nanaomycin A (35). Compound 24, which was prepared in a multistep sequence, underwent acetaldehyde addition to provide exclusively the *cis*-pyran 25 in 51% overall yield after silver(I) oxide treatment. Operating at lower reaction temperatures and omission of the oxidation step led to the isolation of acetal 26. Thus, intramolecular delivery of the acetaldehyde unit rather than direct hydroxyethylation onto the aromatic system is indicated. The *cis*-pyran 25 was converted to nanaomycin A by methyl ether cleavage, acid catalyzed isomerization, and ester hydrolysis.

Similar methodology for pyran ring construction was employed by Kometani and coworkers in 1983 (36). Oxidation of 27 followed by heating induced sulfoxide elimination and Claisen rearrangement to produce 28. Treatment of 28 with

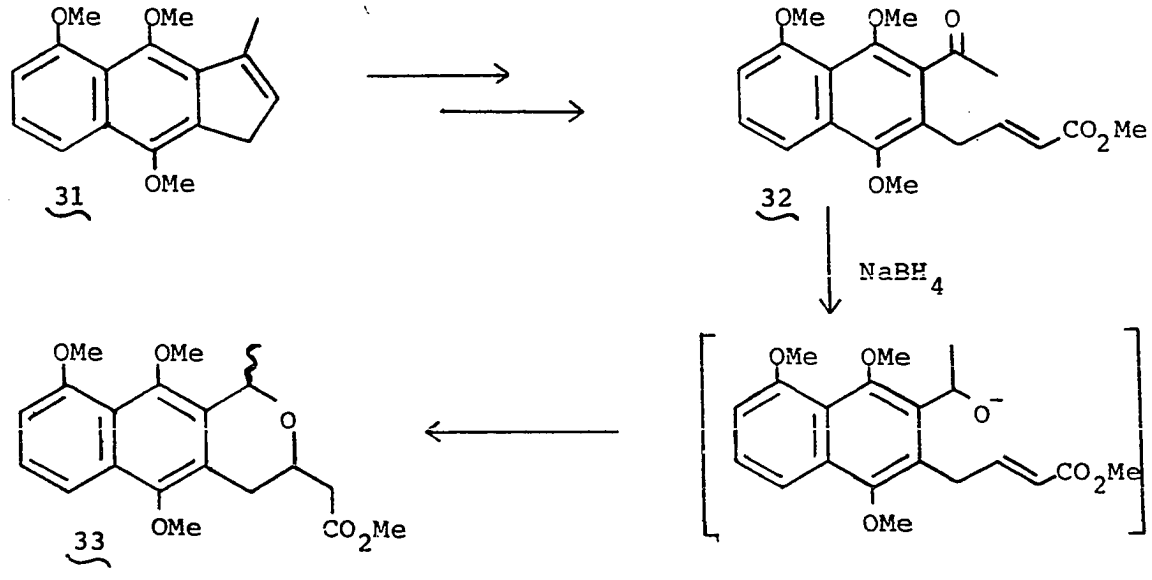


base and oxidative cleavage of naphthofuran 29 afforded 30 in 45% overall yield. Compound 30 was transformed into



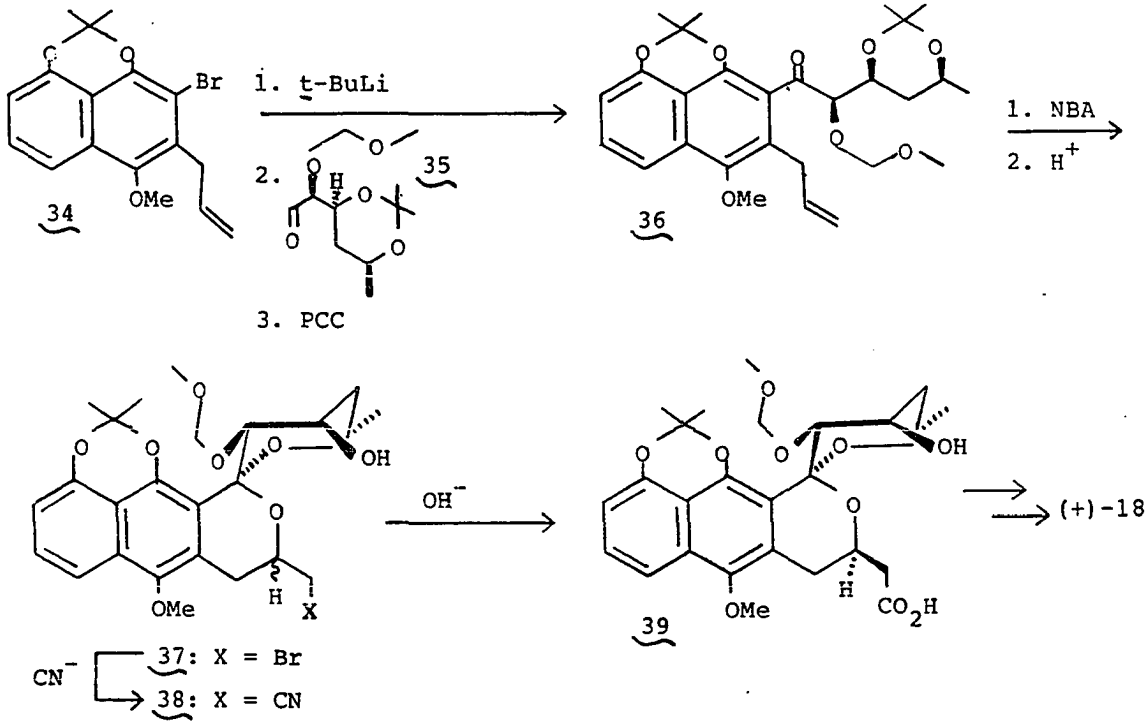
nanaomycin A with reactions similar to those seen in the Li and Ellison synthesis.

The pyran moiety of nanaomycin A has also been constructed via intramolecular alkoxide Michael addition (37). Benzindene 31 underwent Lemieux-Johnson oxidation (periodate-osmium tetroxide) and Wittig olefination to yield 32. Reduction of 32 with sodium borohydride generated an alkoxide which underwent conjugate addition to provide 33 as a 2:1 mixture of pyrans with the trans isomer predominating. A similar route to frenolicin was also reported by Ichihara and coworkers (38).

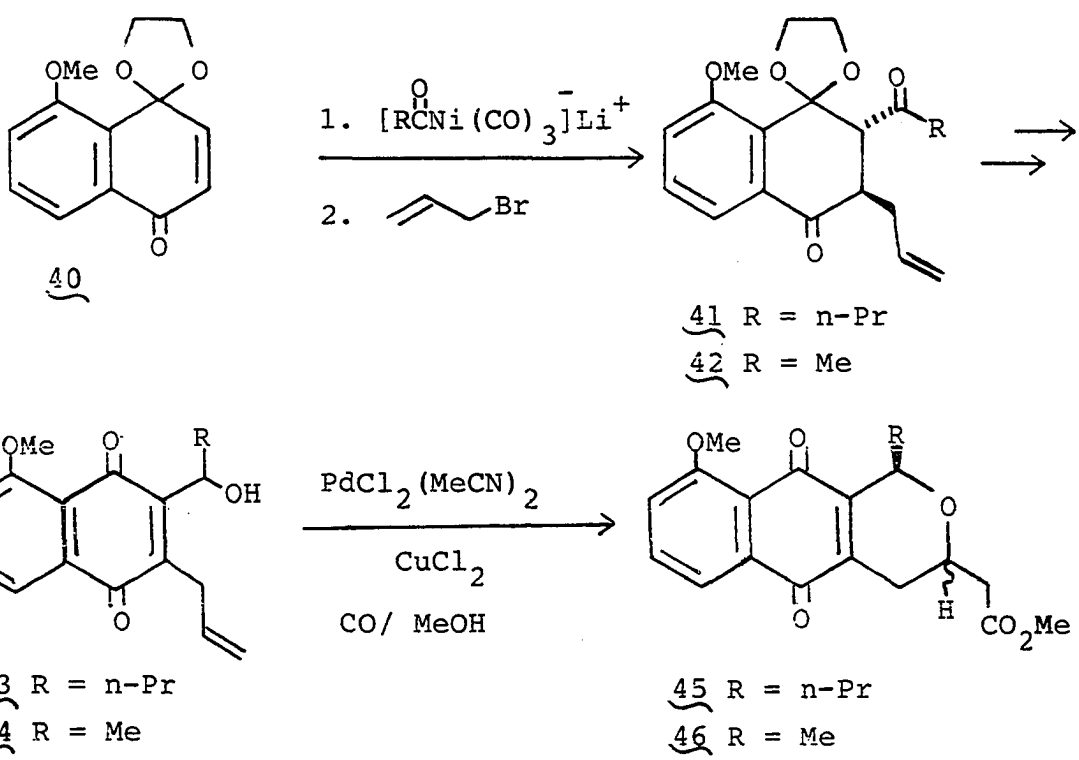


The complex carbon framework of (+)-griseusin A was established by a bisketalization reaction (39). This elegant synthesis, performed by Kometani and coworkers, began with

bromonaphthalene 34. Coupling of the lithio derivative of 34 with the L-dideoxygulose 35 (40) and oxidation afforded 36 in 33% overall yield. Treatment of 36 with N-bromoacetamide (NBA) produced an epimeric mixture of bromohydrins. Exposure of the bromohydrins to protic acid resulted in selective removal of the acetonide protecting group of the sugar moiety and bisketalization yielding 37. After conversion to the nitrile, hydrolysis to the corresponding acid occurred with quantitative epimerization at C-3 (41) affording 39. Conversion of 39 to (+)-griseusin A was easily accomplished in four steps.



Organometallic reactions have played an important role in the preparation of pyranonaphthoquinone antibiotics. In 1982, Semmelhack and coworkers demonstrated the utility of acylate-nickel complexes for the establishment of the isochromane skeleton in nanaomycin A and deoxyfrenolicin (42). Accordingly, the nickel complexes underwent conjugate addition to the juglone monoketal derivative 40 followed by enolate trapping to provide 41 and 42 in high yield. Hydrolysis, to the hydroquinone, reduction, and reoxidation yielded quinones 43 and 44. Reaction of the hydroxyquinones under alkoxycarbonylation conditions (43) provided pyrans 45 and 46.



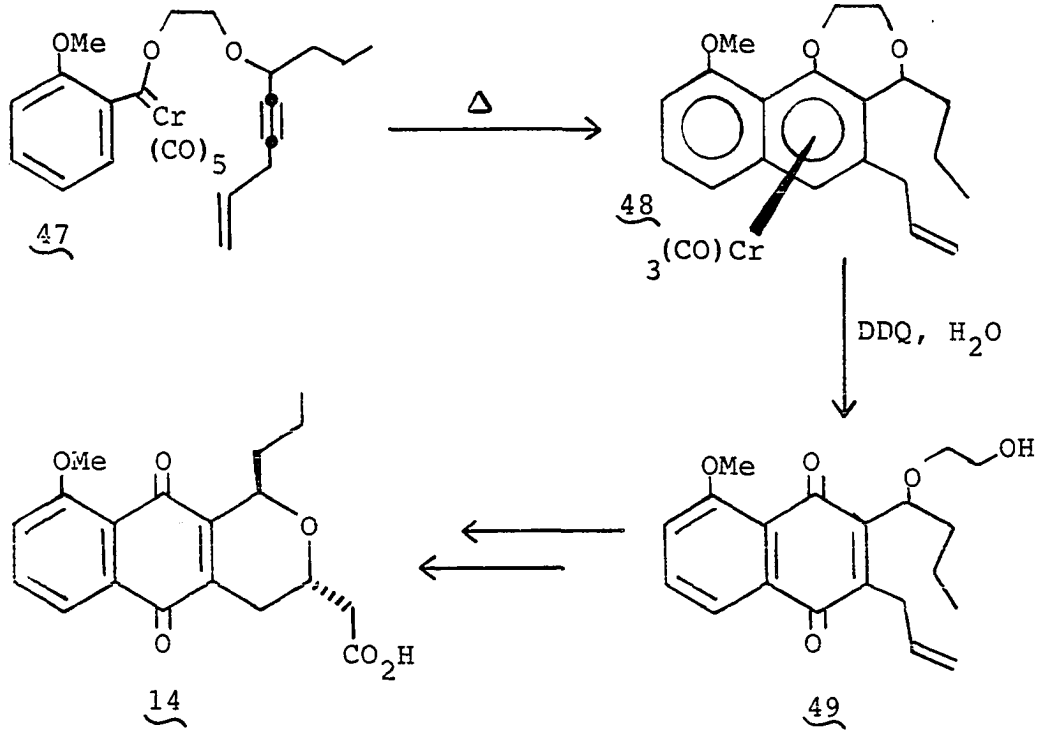
40

41 R = n-Pr
42 R = Me

43 R = n-Pr
44 R = Me

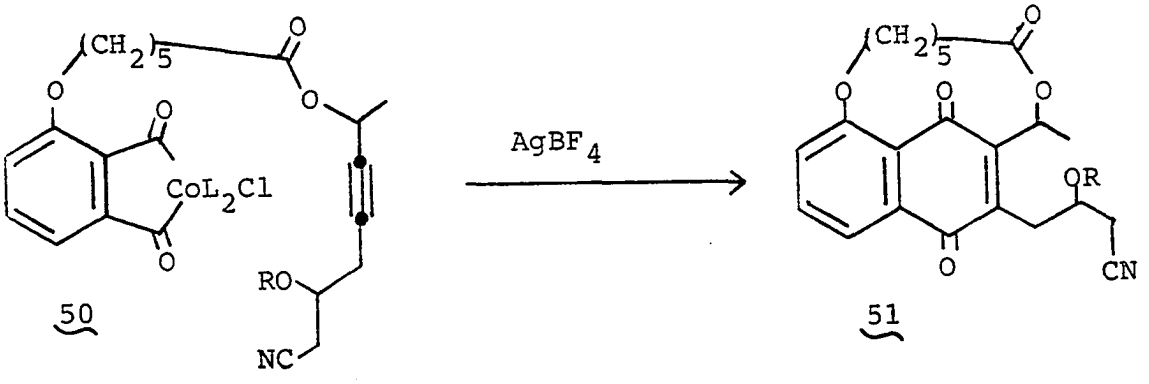
45 R = n-Pr
46 R = Me

A strategy for the synthesis of deoxyfrenolicin based on intramolecular chromium-carbene cycloaddition was also reported by Semmelhack and coworkers (44). Cyclization of 47 occurred under mild conditions to provide the η^6-arylchromium tricarbonyl complex 48. Decomplexation with concomitant oxidation occurred upon treatment with DDQ providing quinone 49. In a five step sequence involving the alkoxycarbonylation reaction, 49 was converted to deoxyfrenolicin.



Another intramolecular cycloaddition route involving organometallic intermediates was reported by South and Liebeskind (45); although in this instance phthaloyl-cobalt

complexes were employed. Complex 50, which was prepared from the corresponding benzocyclobutenedione, and tris(triphenylphosphine)cobalt chloride, does not react upon warming as in the chromium-carbene route. However, treatment with silver(I) tetrafluoroborate opens a coordination site on cobalt and results in an overall insertion-reductive elimination to afford 51 in 47% yield. Conversion of 51 to nanaomycin A was accomplished in three steps involving reductive pyran formation and hydrolysis of the nitrile.

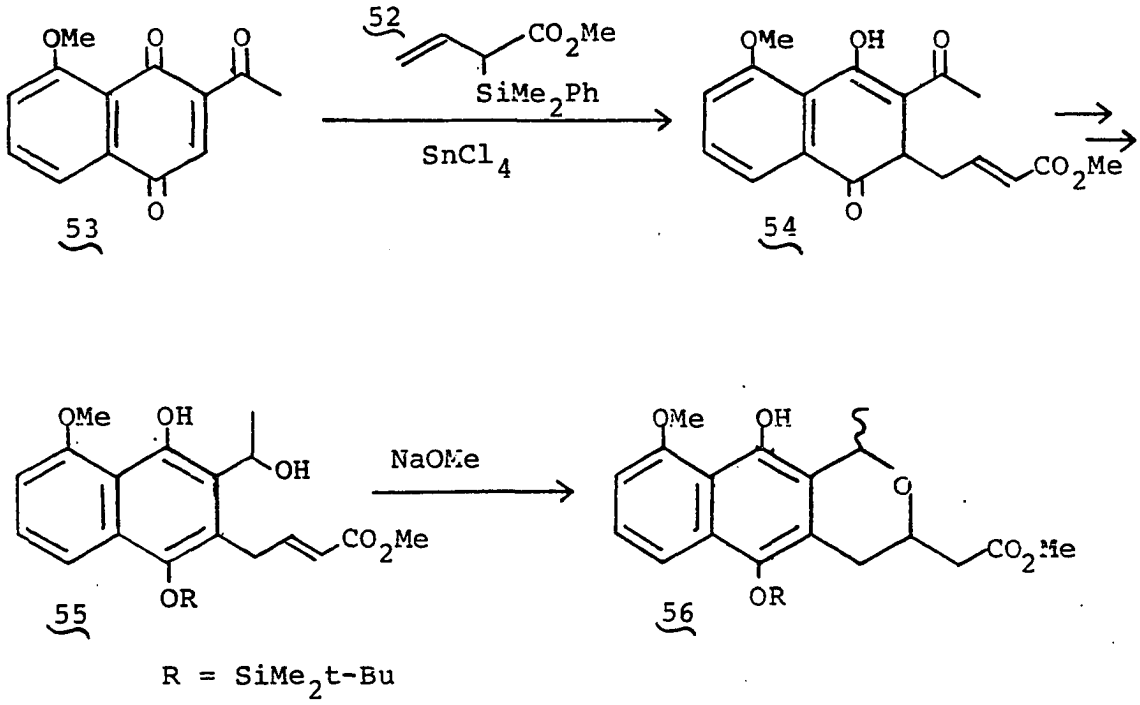


50 51

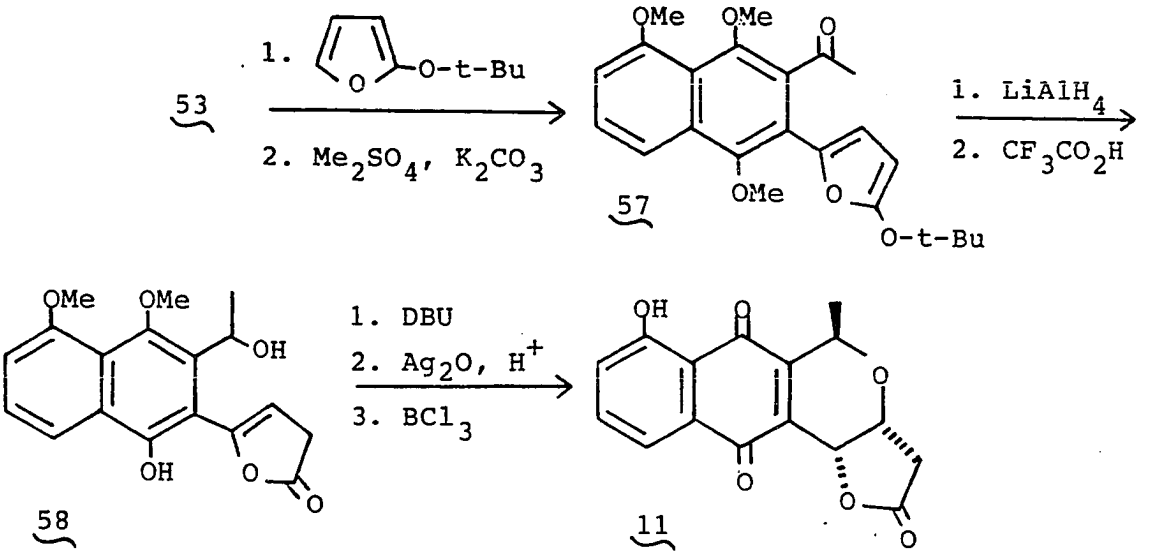
L = PPh_3, R = $SiMe_2t$-Bu

The addition of enolate equivalents to acylnaphthoquinones constitutes a particularly facile route to the pyranonaphthoquinone antibiotics. Naruta and coworkers have shown that 2-silylbutenoate esters react only from the gamma position (46). Exploiting this selectivity, reaction of silylbutenoate 52 with the activated naphthoquinone 53 in the presence of tin tetrachloride produced 54. After aromatization, phenol

protection, and reduction, base promoted alkoxide Michael addition afforded 56 as a 1:1 mixture of cis and trans pyrans (47).



In 1978, Kraus and Roth reported a direct synthesis of racemic 9-deoxykalafungin utilizing a 2-alkoxyfuran as a masked butenolide anion (48). Later, racemic kalafungin itself was prepared by this route. Thus, 53 underwent Michael addition without the aid of catalysis to produce naphthalene 57 after aromatization and phenolic methylation. Reduction followed by hydrolysis afforded butenolide 58. Ring closure to the pyrano-γ-lactone, oxidation, and phenolic demethylation yielded kalafungin in excellent overall yield

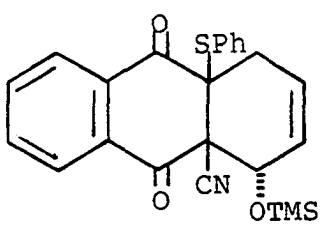


(49). It is noteworthy that during the oxidative demethylation step, the initially produced epimeric mixture of pyranolactones were completely equilibrated to the natural configuration.

In summary, the pyranonaphthoquinones are a valued group of antimicrobial agents. Their unique structure and biological activity has prompted considerable synthetic attention. Many elegant syntheses of these compounds have been achieved; however, the problem of initial stereocontrol in pyran ring construction remains largely unsolved. Although the approaches involving organometallic intermediates are highly convergent, the synthetic routes involving nucleophilic additions to activated naphthoquinones are the most direct and practical.

RESULTS AND DISCUSSION

Our synthetic approach to the pyranonaphthoquinone antibiotics stemmed from the earlier observation (Part II) that blocked anthraquinone tautomers such as 59 and 60 underwent facile retro-aldol and retro-Claisen reactions upon treatment with aqueous base.



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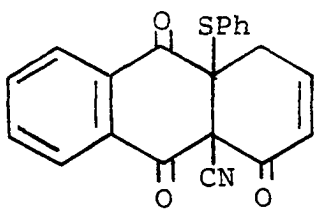
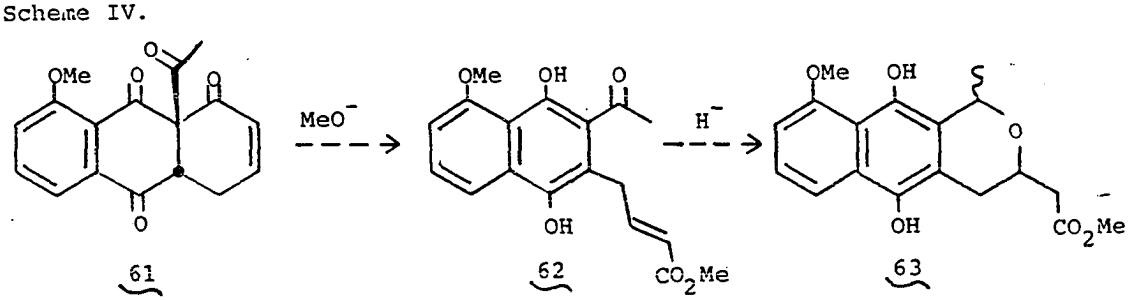


60

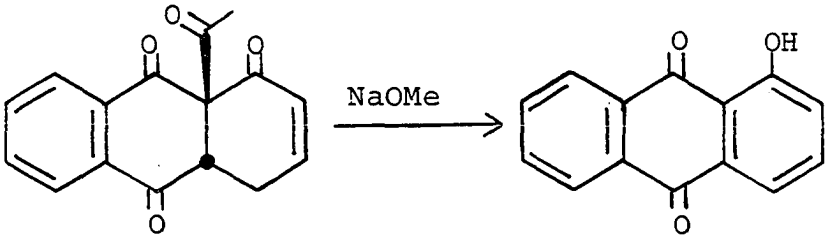
We anticipated that the semi-blocked anthraquinone tautomer 61 would behave similarly (Scheme IV). If this were the case, then cleavage with methoxide anion would provide 62. Reduction and intramolecular alkoxide addition would afford 63, an excellent precurser to nanaomycins A and D.

Scheme IV.



61 62 63

To test this approach, diketone 64 was treated with sodium methoxide. Upon workup, however, only anthraquinone 65 resulting from undesired cleavage of the acetyl group and aerial oxidation was isolated. A variety of other conditions



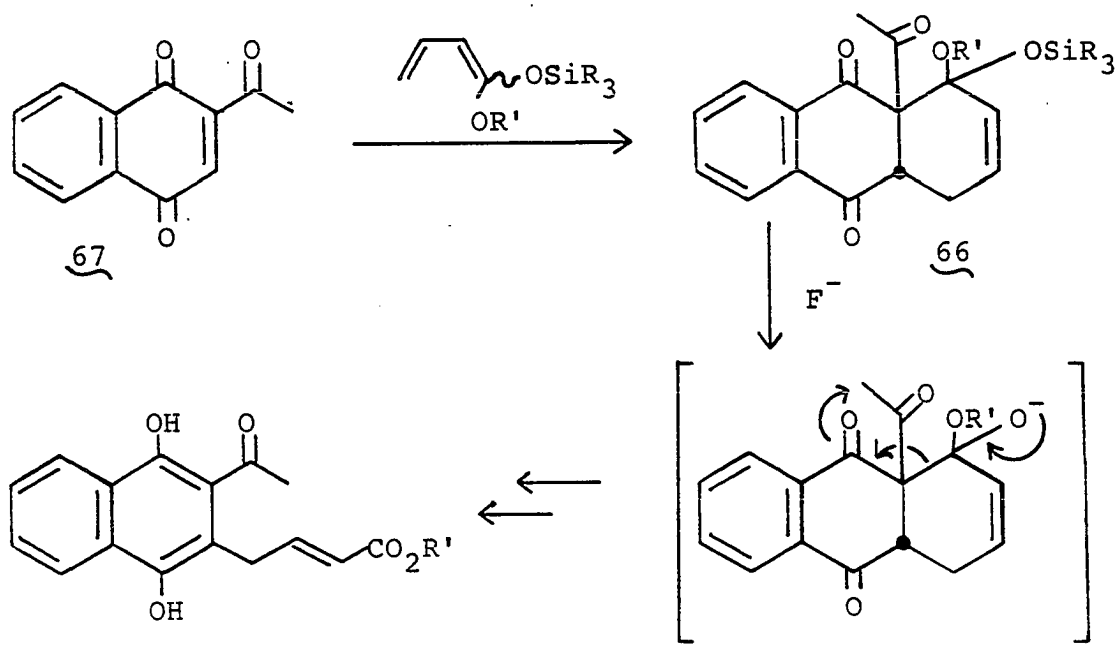
64 65

including acidic catalysis were attempted, unfortunately none of the desired ring-cleavage product could be detected.

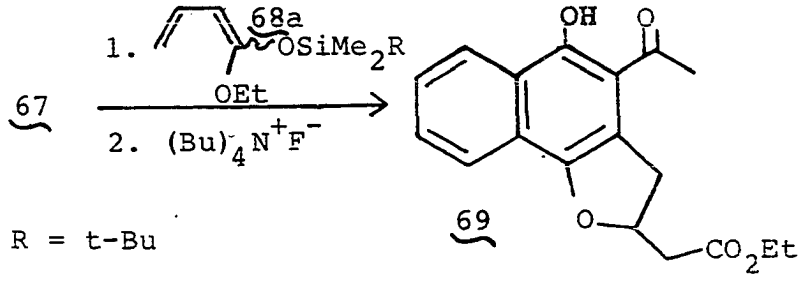
In view of these results, a method to site-specifically generate the requisite tetrahedral intermediate was needed. A mixed ketal such as 66 appeared promising. Following its generation via a Diels-Alder reaction, fluoride induced cleavage of 66 would produce the desired transformation (Scheme V).

Reaction of acetylnaphthoquinone 67 (50) with 1-ethoxy-1-tert-butyldimethylsilyloxybutadiene 68a (51) was rapid. Due to the known instability of mixed ketals (52,53), the presumed Diels-Alder adduct was treated with tetrabutylammonium fluoride. Surprisingly, upon workup, dihydronaphthofuran 69 was isolated in good yield.

Scheme V.



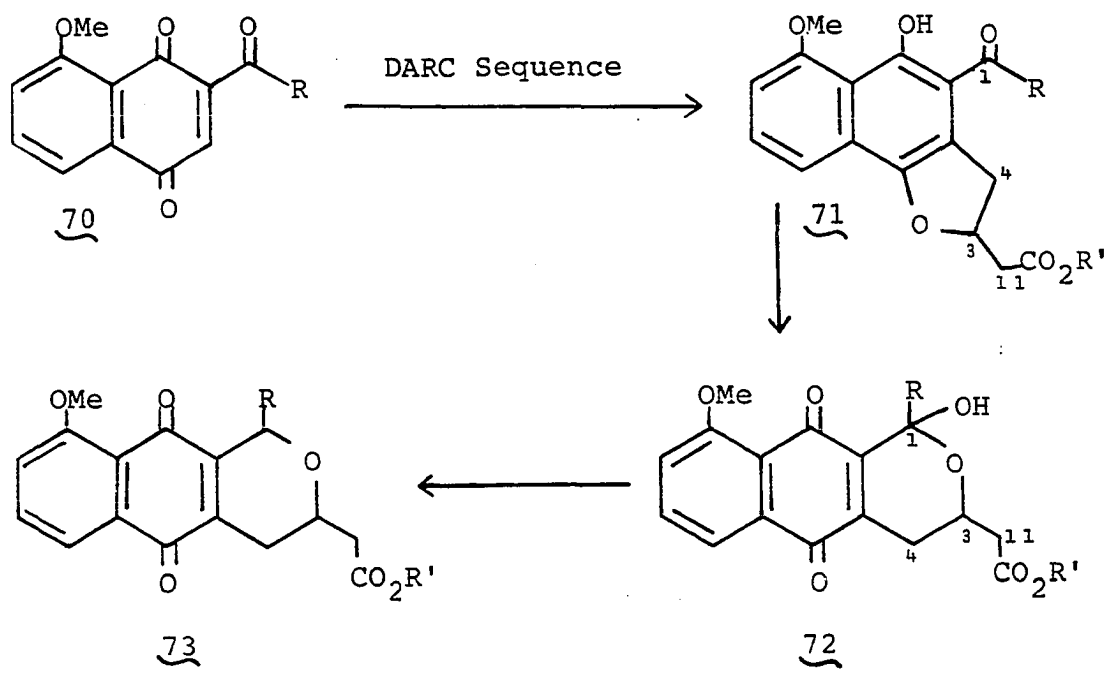
Apparently, the cis crotonate subunit that was liberated by the retro-Claisen reaction rapidly reacted with the neighboring phenol to produce 69. This cyclization had previously been observed by Naruta and coworkers (47) in their synthetic studies toward the pyranonaphthoquinones. To avoid this "undesirable" cyclization, they protected the phenol.



Although other workers viewed the formation of dihydronaphthofuran products as undesirable, we envisioned the

Diels-Alder/retro-Claisen (DARC) sequence as a synthetically useful transformation. Indeed, a new approach to the pyranonaphthoquinone antibiotics was formulated based on this new reaction sequence. Our strategy is outlined in Scheme VI.

Scheme VI.

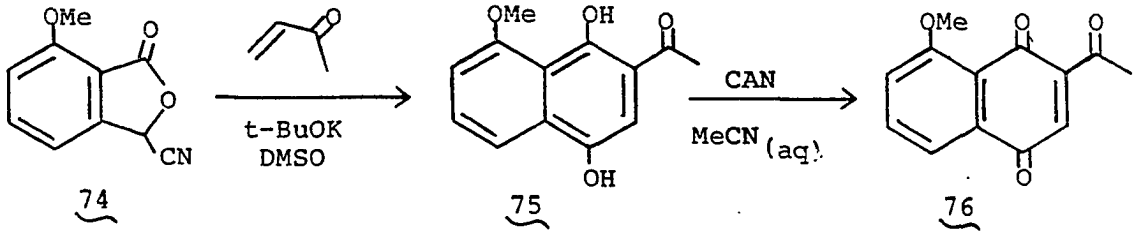


70 71 73 72

Anticipating that the new Diels-Alder/retro-Claisen (DARC) sequence would be general, an alkoxy substituted acylnaphthoquinone such as 70 would produce 71. Oxidative dealkylation and subsequent attack of the liberated 3-hydroxyl group at the C-1 carbonyl was expected to afford hemiketal 72. Finally, selective reduction of the hemiketal would yield 73.

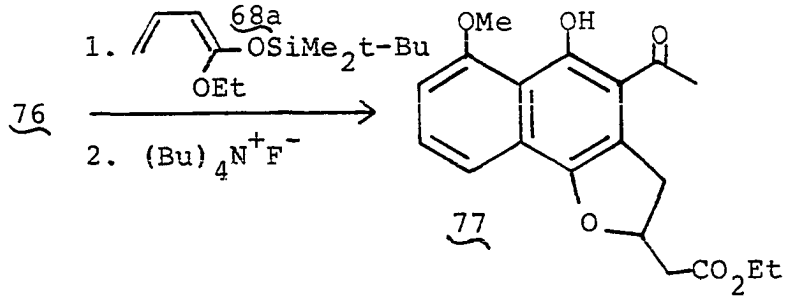
The known 8-methoxy-2-acetyl-1,4-naphthoquinone 76 (54) was prepared employing improved cyanophthalide annulation

conditions (49). Thus, treatment of cyanophthalide 74 (55) with methyl vinyl ketone and potassium tert-butoxide in dimethylsulfoxide produced multigram quantities of hydroquinone 75 in 65-70% yield. Oxidation to quinone 76 was effected in nearly quantitative yield with ceric ammonium nitrate (CAN) (56). Performing the DARC sequence with 76 and



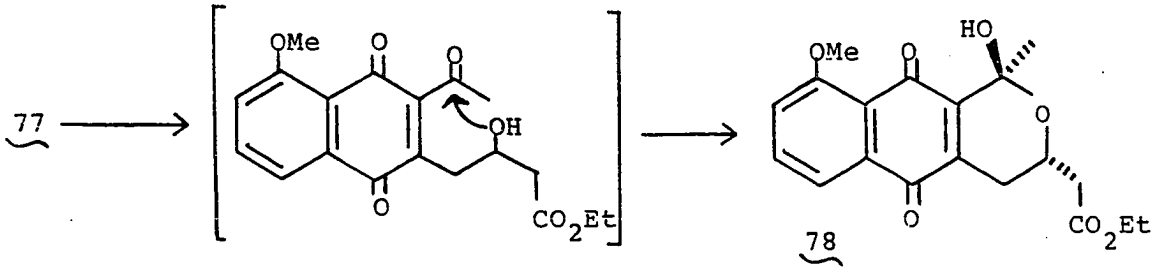
74 75 76

diene 68 generated 77 in high yield. Naphthoquinone 76 is somewhat unstable and in practice it was submitted, without additional purification, to the DARC sequence to provide 77 in 76-78% yield from 75.



Oxidative dealkylation (57) of 77 occurred upon treatment with CAN in aqueous acetonitrile at ambient temperature. The

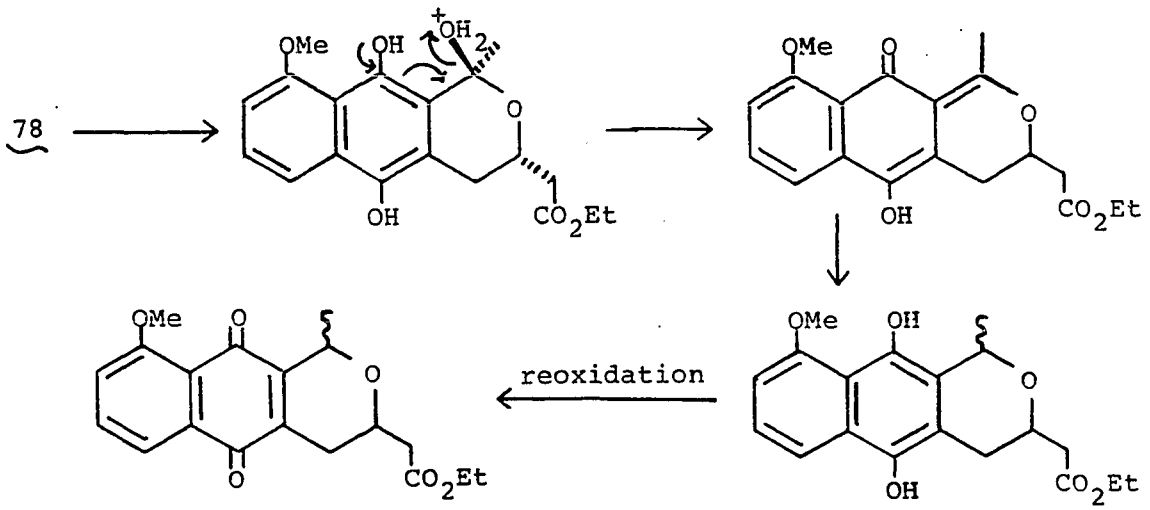
product, produced in 91% yield as a single diastereomer, was assigned structure 78 based on its spectroscopic data. The 300 MHz ^{1}H NMR spectrum of 78 showed a geminally coupled



doublet of doublets (J = 18.6 and 2.7 Hz) at 2.88 ppm, and a similar resonance at 2.27 ppm with a vicinal coupling constant of 11.1 Hz. By selective irradiation experiments, these signals were assigned to the pyran methylene protons. A signal at 94.2 ppm in the broad-band noise decoupled ^{13}C spectrum was indicative of a hemiketal unit (58). These observations are consistent with a pseudoequatorial disposition of the acetic ester moiety, and assuming a strong anomeric effect, a pseudoaxial hemiketal hydroxyl group. These assignments were confirmed by a single crystal X-ray structure of a closely related hemiketal (vide infra).

We next turned our attention to the critical hemiketal reduction. To realize this goal, we envisioned reduction of the quinone moiety in 78 to a naphthhydroquinone followed by expulsion of water and conjugate hydride addition (Scheme VII). Treatment of 78 with zinc dust in acetic acid (59)

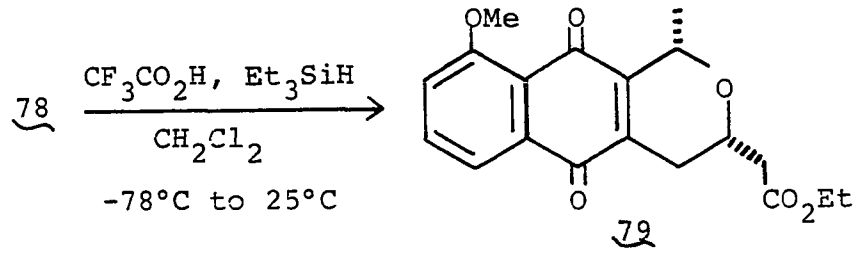
Scheme VII.



resulted in a rapid decolorization of the solution indicative of hydroquinone formation. Unfortunately, upon reoxidation with CAN, none of the desired pyran was formed. Catalytic hydrogenolysis with palladium on charcoal (60) also failed.

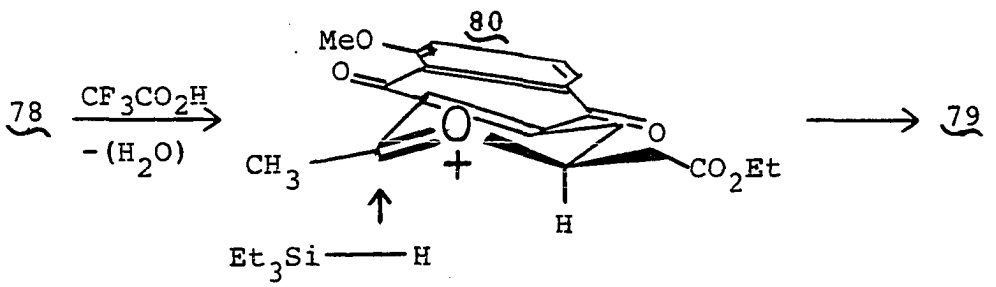
If reduction of the naphthoquinone unit in 78 was accompanied by hemiketal ring opening, further reduction to a pyran would be difficult. Ionic hydrogenation has been employed by several researchers to reduce acetals, hemiketals, and some alcohols (61-63). Additionally, naphthoquinones and anthraquinones are reduced with difficulty under standard ionic hydrogenation conditions (H^+/R_3SiH) (64). Thus, ionic hydrogenation appeared promising for selective reduction of the hemiketal unit in 78.

In the event, treatment of 78 with triethylsilane and trifluoroacetic acid proceeded stereospecifically to afford the cis-pyran 79 in quantitative yield.

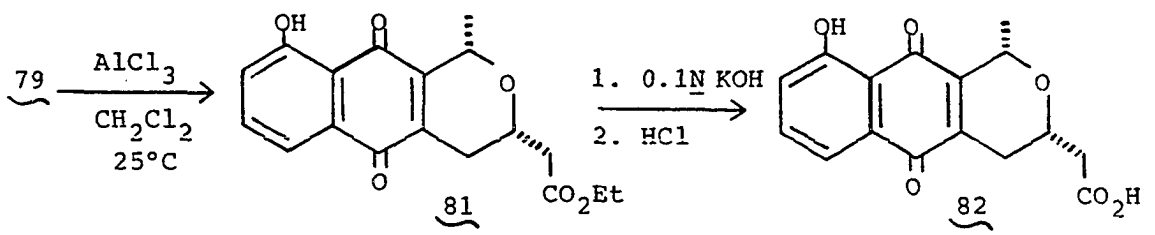


The assignment of cis stereochemistry to 79 was based on its ^1H NMR spectrum. At 300 MHz, the methylene protons of the pyran ring gave rise to two ddd patterns at δ 2.83 (pseudoequatorial H as an apparent dt with J = 18.1, 2.5, and 2.5 Hz) and δ 2.28 (pseudoaxial H with J = 18.1, 10.5, and 3.7 Hz) which are identical with regard to multiplicity and magnitudes of coupling constants to the corresponding methyl ester reported by others (37, 44).

The observed stereospecificity is best explained by the initial formation of a transient oxonium ion 80. This oxonium ion then preferentially accepts hydride from the α (axial) side due to the anomeric effect (65) from the ring oxygen. Axial hydride delivery to cyclic oxonium ions such as 80 is well precedented (66, 67). Additionally, carbon nucleophiles such as allylic silanes take a similar stereoelectronic course in reactions with cyclic oxonium ions (67-69).



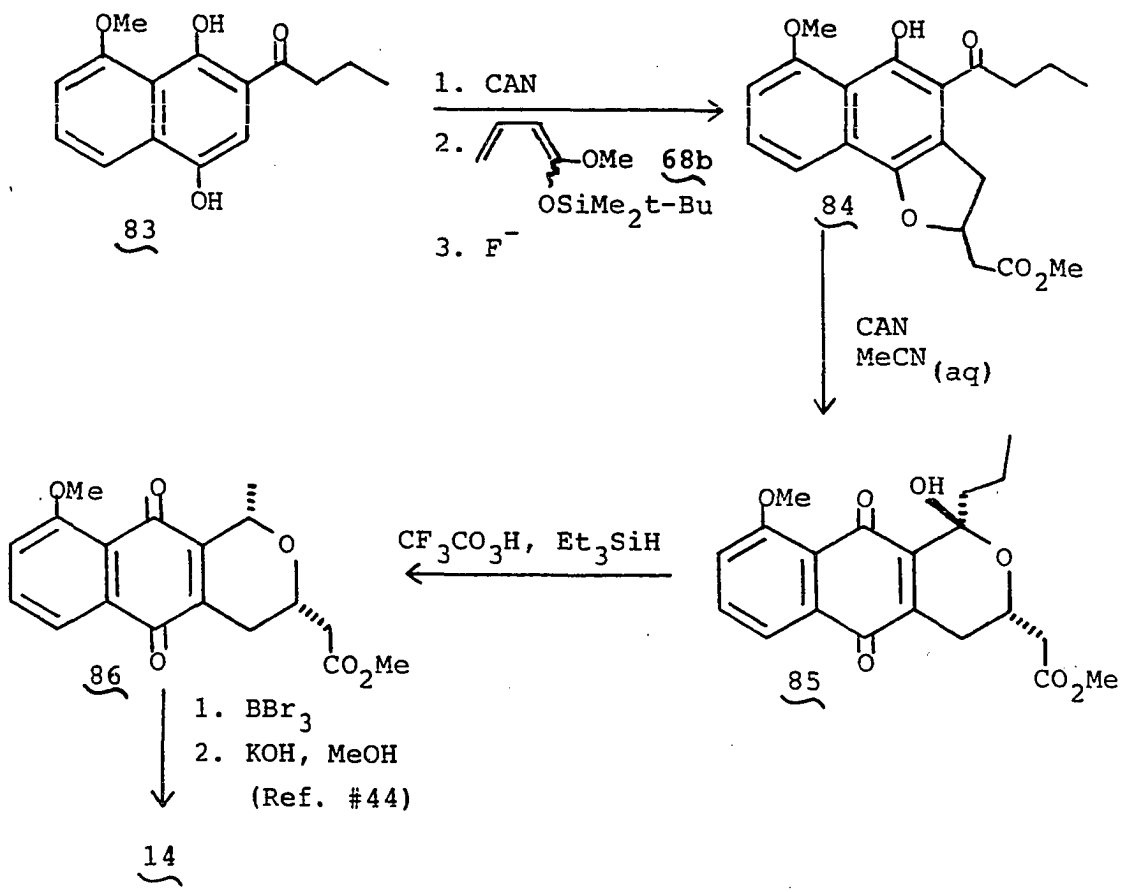
Compound 79 has previously been converted to nanaomycin by Li and Ellison (35). Although the melting point of 79 corresponds well with that reported by Li and Ellison, a comparison of spectral data was impossible. For this reason, 79 was converted to racemic epinanaomycin A, a well characterized compound. Phenolic demethylation produced 81 in 94% yield.



Saponification afforded epinanaomycin A 82 which was identical in every respect with the analytical data reported by others (45, 47).

The synthesis of deoxyfrenolicin paralleled that of nanaomycin A and is depicted in Scheme VIII. Phthalide annulation with 1-hexen-3-one produced 83 in an unoptimized

Scheme VIII.



yield of 59%. Performing the DARC sequence with 1-methoxy-1-tert-butyldimethylsilyloxy-1,3-butadiene (70) afforded dihydronaphthofuran 84 in 70% overall yield from 83. Oxidative dealkylation of 84 occurred in 94% yield. Single crystal X-ray analysis of 85 clearly indicated that the hemiketal hydroxyl group was in a pseudoaxial position (Figure 3) (71). Ionic hydrogenation of 85 occurred in 84% yield to afford exclusively the cis-pyran 86.

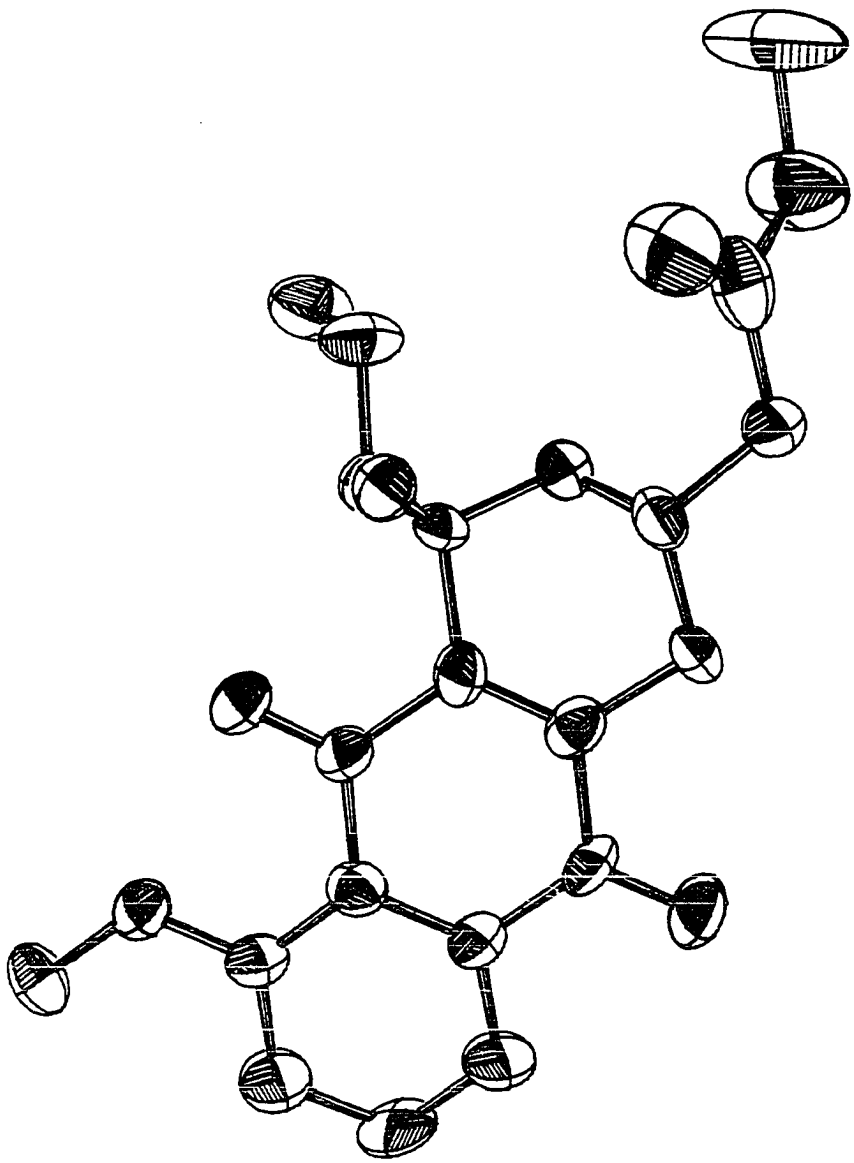


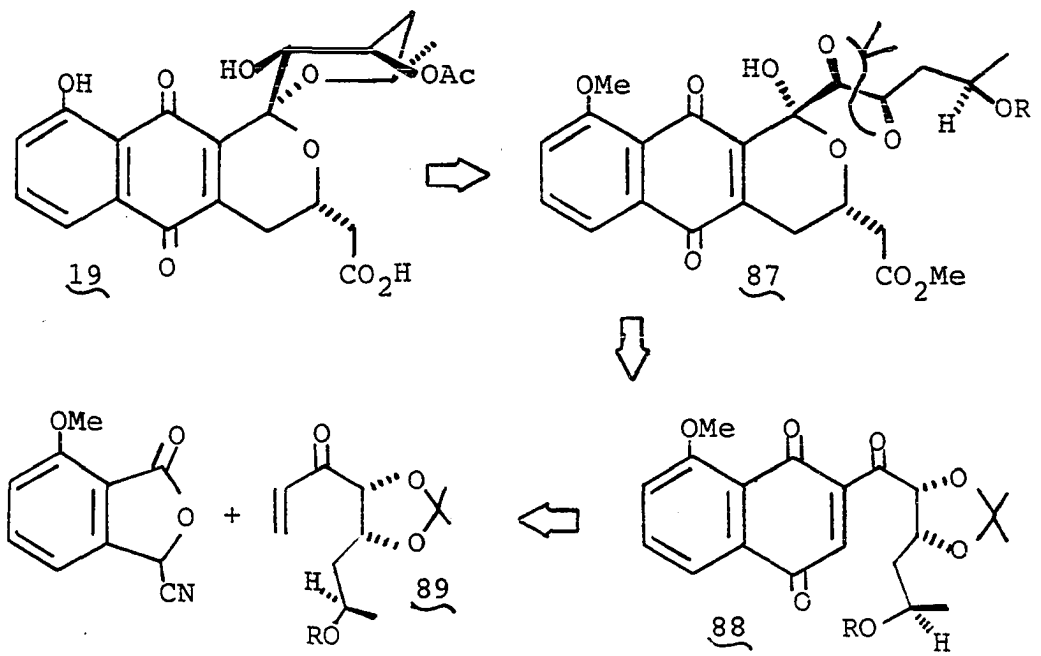
Figure 1. X-ray crystal structure of 85

The spectroscopic data and melting point of 86 were identical with that of the cis-pyran reported by Semmelhack et al. (44). Since 86 has been converted to deoxyfrenolicin by demethylation accompanied by complete isomerization to the trans isomer, and saponification, a formal synthesis of deoxyfrenolicin is completed.

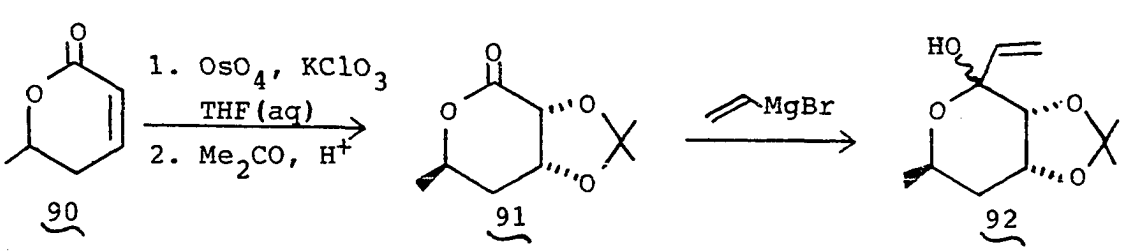
Our next goal was a total synthesis of griseusins A and B. Since the γ-lactone unit of griseusin A is established by aerial oxidation of griseusin B (21), the latter compound was our immediate target. We envisioned that the spiroketal moiety of griseusin B would result from the selective deprotection of the secondary alcohol (OR) in 87. This compound would result from the DARC sequence performed on 88 followed by oxidative dealkylation. In keeping with our earlier starting material preparations, phthalide annulation with an enone, such as 89, would be employed. Our retrosynthetic plan for the construction of griseusin B is depicted in Scheme IX.

The correct relative stereochemistry for the northern half of the spiroketal unit in 19 was established from readily available parasorbic acid 90 (72). Hydroxylation (73) followed by treatment of the crude diol with acidic acetone afforded the known ribo-hexonic acid δ-lactone derivative 91 (74). To prepare 89, we envisioned lactone ring opening with a vinyl Grignard reagent (75) followed by protection of the

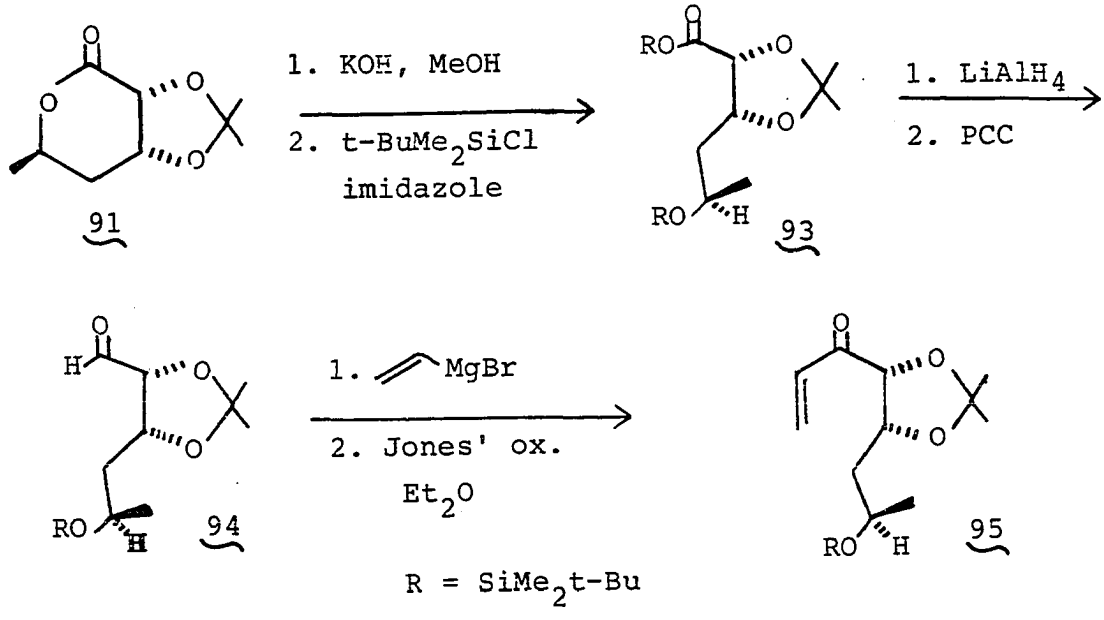
Scheme IX.



liberated secondary alcohol. However, treatment of 91 with vinyl magnesium bromide or vinyl lithium under a variety of conditions did not afford any of the desired enone. In every instance, an anomeric mixture of hemiketals 92 were produced. Additionally, all attempts to induce ring opening with concomitant alcohol protection failed.

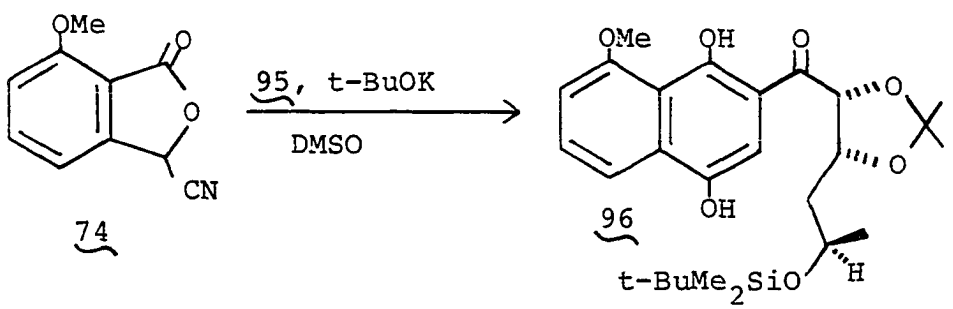


In view of these results, a route to enone 89 involving protection of the secondary alcohol prior to enone formation was developed. Saponification of 91 followed by silylation of the potassium salt (76) produced the bisprotected ester 93 in high yield. Reduction to the primary alcohol and reoxidation afforded aldehyde 94 in 66% overall yield. Finally, Grignard addition followed by two-phase Jones' oxidation (77) produced enone 95 in moderate yield. However, the six step preparation of 95 could be conducted in 15% overall yield from 91 without purification of intermediates.



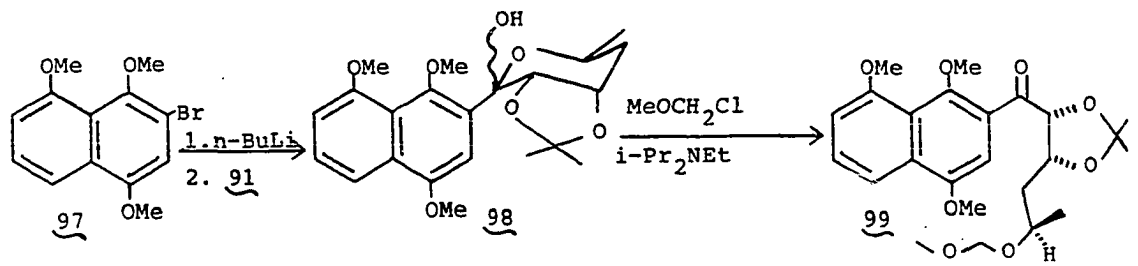
With ample quantities of 95 available, the preparation of the complex acylnaphthoquinone was undertaken. Unfortunately,

phthalide annulation with 95 proved difficult; affording 96 in only 15% yield. Variation of the protecting group at the C-2 position of 95 did not produce better yields of the annulation product, and in one instance (R = CH_2OCH_3) the annulation failed completely.

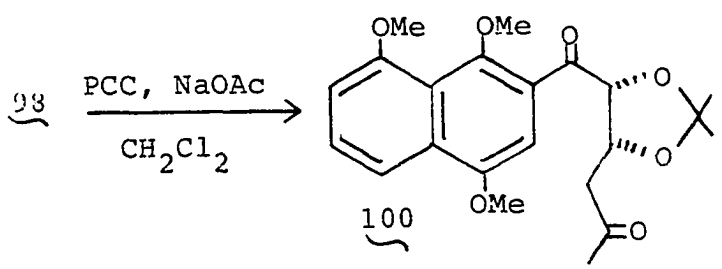


Evidently, the strongly basic conditions of the phthalide annulation promoted β-elimination of the acetonide unit in 95 and the annulation product.

In view of the poor yields obtained above, an alternative route to 88 involving milder conditions was probed. Metallation of 97 (78) followed by treatment with lactone 91 afforded a mixture of ketals 98. Unlike the earlier vinyl Grignard addition product, treatment with chloromethyl methyl ether and Hünig's base effected ring opening and protection of the C-2 alcohol in 45% overall yield. Unfortunately, CAN oxidation of 99 failed, producing highly polar uncharacterizable materials. Additionally, oxidative demethylation employing Rapoport's procedure (AgO, 6N HNO_3) (79) was also



ineffective. Rationalizing that the failure of the oxidation was due, at least in part, to the lability of the protecting group at C-2; the diketone 100 was prepared by oxidation of 98. Regrettably, its oxidation also failed. At this point

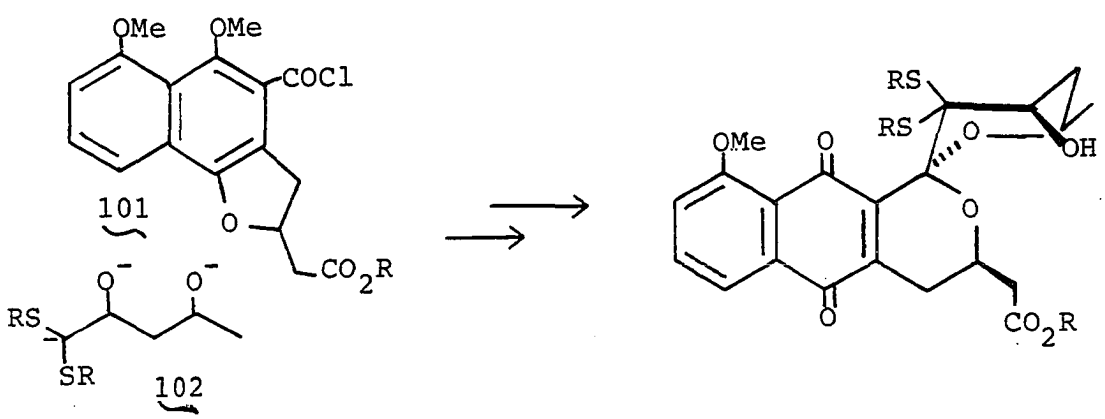


we were convinced that the acetonide group was being cleaved due to the acidic conditions required for oxidation (80). A ready solution to this problem could not be found, thus a complete change in strategy was necessary.

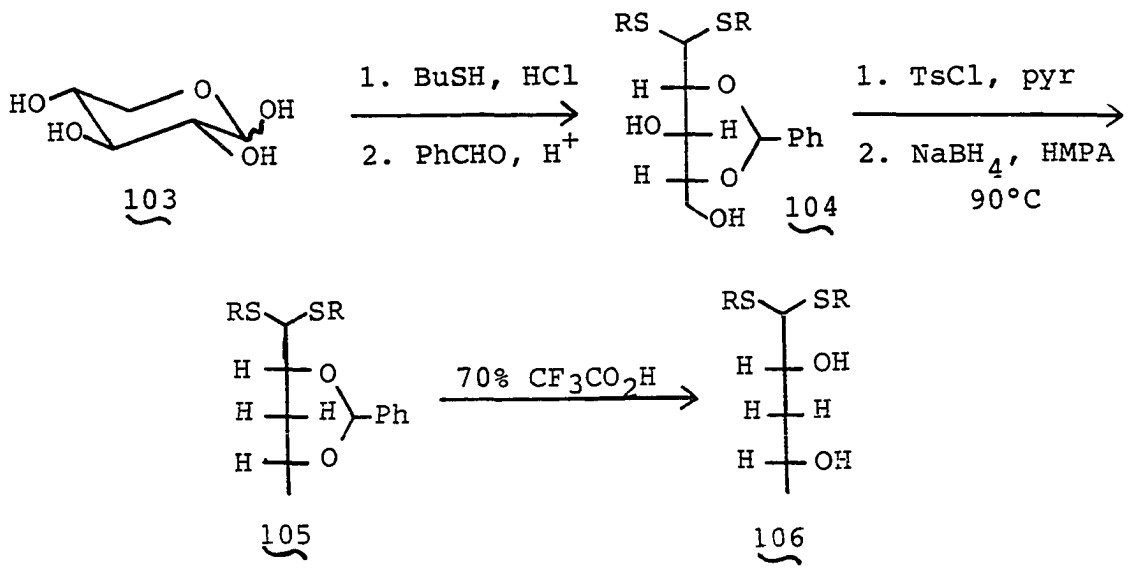
Toward this end, the coupling of a five carbon carbohydrate derivative to an intact DARC product was envisioned (Scheme X). In order to alleviate the problems of protecting group instability, a trianion such as 102 was chosen. Literature precedent indicated that 102 would

preferentially attack electrophiles from the dithioketal position (81,82). After monoaddition, CAN oxidative dealkylation was anticipated to occur with concomitant spiroketalization (39). Additionally, a coworker from these laboratories had demonstrated that the DARC sequence could be carried out with carboalkoxynaphthoquinones (83). Thus, the obtention of an acid chloride such as 101 seemed likely.

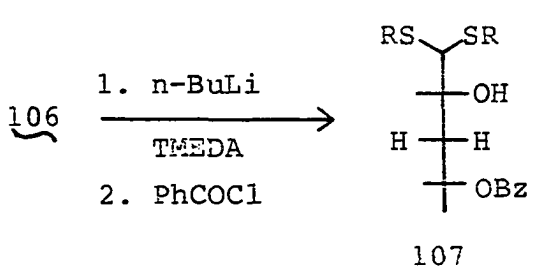
Scheme X.



For use in model system studies, D-xylose was chosen as the carbohydrate starting material. Thioketalization followed by selective formation of the most hindered benzylidene acetal (84) afforded 104 (85). To produce the 3,5-dideoxythioketal, 104 was tosylated and deoxygenated with sodium borohydride in hexamethylphosphoric triamide (86) to produce 105 in 39% yield. Finally, hydrolysis of the benzylidene protecting group occurred selectively (87) to afford 106 in 66% yield.



To test our new strategy, we employed benzoyl chloride as a model electrophile. Unfortunately, after treatment with a slight excess of n-butyllithium and quenching the presumed trianion with benzoyl chloride, only ester 107 was isolated. Despite several experimental modifications, only products of alkoxide attack on the acid chloride were obtained. Evidently, metallation of the thioacetal is not favored, perhaps due to steric reasons (88).



Fortunately, 1,3-dithianes are readily metallated regardless of the alkyl group present (89). Efforts to prepare the 1,3-dithiane analog of 106 are currently in progress.

EXPERIMENTAL

General

Unless otherwise noted, materials were obtained from commercial suppliers and were used without purification. THF and diethyl ether were distilled from sodium benzophenone ketyl under nitrogen prior to usage. Benzene was distilled from lithium aluminum hydride. Dichloromethane was distilled from calcium hydride. Unless otherwise noted, all reactions were conducted under an argon atmosphere. Unless otherwise noted, all organic extracts were dried over anhydrous sodium sulfate. Melting points were determined on a Fisher-Johns melting point apparatus and are uncorrected. Infrared spectra were obtained on a Beckman IR-4250 or a Perkin-Elmer model 1320 spectrophotometer. Nuclear magnetic resonance spectra were determined on a Varian EM-360 spectrometer. High field (300 MHz) proton spectra were obtained with a Nicolet Magnetics Corporation NMC-1280 spectrometer. All chemical shifts are reported in δ relative to tetramethylsilane as an internal standard. Coupling constants (J) are reported in Hz. Abbreviations: s = singlet, d = doublet, t = triplet, q = quartet, bs = broad singlet, m = multiplet, ABq, AB quartet. Carbon-13 NMR spectra were determined on a Nicolet NMC-1280 spectrometer and are reported in ppm relative to the central peak of $CDCl_3$ (77.06 ppm). High-resolution mass spectra were recorded on a Kratos model MS-50 spectrometer. Low-resolution

mass spectra were recorded on a Finnegan 4023 mass spectrometer. Silica gel used for flash chromatography (90) was 230-400 mesh (Kieselgel 60) purchased from EM Science. Gravity column chromatography was performed on 60-200 mesh silica gel purchased from Davison Chemical (WR Grace Inc.). Elemental analyses were performed by Galbraith Laboratories, Inc.

Ethyl[5-Acetyl-6-hydroxy-3,4-dihydronaphtha[1,2-b] furan-3-yl]acetate (69)

To a solution of 2-acetyl-1,4-naphthoquinone (160 mg, 0.80 mmole) in 10 mL of methylene chloride at -78°C was added 1-ethoxy-1-(tert-butyldimethylsilyl)oxy-1,3-butadiene (370 mg, 1.60 mmole) in 0.5 mL of methylene chloride. The solution was warmed slowly to ambient temperature over 30 minutes, and was then recooled to 0°C. The reaction mixture was then treated sequentially with 5 mL of acetonitrile, 2 mL of a pH = 7.5 phosphate buffer, and tetra-n-butylammonium fluoride (1.6 mL of a 1.0 M solution in THF). The mixture was slowly warmed to ambient temperature and made slightly acidic with 2 N HCl. The resulting two-phase mixture was poured into 50 mL of brine and extracted with three 20 mL portions of diethyl ether. The organic extracts were combined, washed with brine, and dried. The solvents were removed in vacuo and the residue of flash chromatographed on silica gel eluting with 3:1 hexanes/ethyl acetate to afford 175 mg (70%) of 69 : mp 103-104°C; 300 MHz

^{1}H NMR ($CDCl_3$) δ 1.27 (t, 3 H, J = 7.2 Hz), 2.42 (s, 3 H), 2.68 (dd, 1 H, J = 16.5 Hz, and 6.9 Hz), 2.90 (dd, 1 H, J = 16.5 and 6.9 Hz), 3.09 (dd, 1 H, J = 15.6 and 7.2 Hz), 3.53 (dd, 1 H, J = 15.6 and 11.1 Hz), 4.18 (m, 2 H), 5.16 (m, 1 H), 7.41 (t, 1 H, J = 8.1 Hz), 7.52 (t, 1 H, J = 7.2 Hz), 7.21 (d, 1 H, J = 8.4 Hz), 8.29 (d, 1 H, J = 8.1 Hz), 14.16 (s, 1 H); IR ($CDCl_3$) 3055, 2980, 1725, 1610, 1580, 1450, 1250, 1150, 1010, 840 cm^{-1}; ^{13}C NMR 14.15, 30.86, 39.60, 40.94, 60.83, 78.32, 111.15, 114.01, 121.23, 124.72, 124.91, 125.92, 129.97, 146.78, 158.69, 170.43, 203.60 ppm; MS m/e 314, 269, 226; high resolution mass spectrum for $C_{18}H_{18}O_5$ requires 314.11543, determined 314.1149.

2-Acetyl-1,4-dihydroxy-8-methoxynaphthalene (76)

To a solution of phthalide 74 (2.15 g, 11.37 mmole) and methyl vinyl ketone (1.04 mL, 12.5 mmole) in 57 mL of dimethylsulfoxide at ambient temperature was added potassium tert-butoxide (1.945 g, 17.35 mmole). After stirring 90 minutes at ambient temperature an equal portion of potassium tert-butoxide was added and stirring continued for 90 min. The reaction mixture was diluted with 30 mL of diethyl ether and acidified with excess 2 N HCl. The resulting yellow solution was poured into 500 mL of ice water and extracted 8 times with 50 mL portions of diethyl ether. The organic extracts were combined, washed with brine, and dried. The solvents were removed in vacuo and the residue chromatographed

on 175 g of silica gel eluting with 2.5:1 hexanes/ethyl acetate to afford 1.74 g (66%) of 76: 300 MHz ^{1}H NMR ($CDCl_3$) δ 2.65 (s, 3 H), 4.05 (s, 3 H), 6.96 (d, 1 H, J = 7.8 Hz), 7.16 (s, 1 H), 7.54 (t, 1 H, J = 8.1 Hz), 7.82 (d, 1 H, J = 8.1 Hz), 8.14 (s, 1 H), 13.6 (s, 1 H); IR ($CDCl_3$) 3600-3400, 1640, 1600 cm^{-1}.

Ethyl[5-Acetyl-6-hydroxy-7-methoxy-3,4-dihydronaphtha[1,2-b]furan-3-yl]acetate (77)

To a solution of 76 (540 mg, 2.32 mmole) in 25 mL of acetonitrile at ambient temperature was added ceric ammonium nitrate (2.92 g, 5.34 mmole) in 4 mL of water. After stirring 20 minutes at ambient temperature, the reaction mixture was diluted with 20 mL of methylene chloride and poured into 100 mL of water containing 10 mL of a 1 M pH = 7.2 phosphate buffer. The layers were separated and the aqueous phase was extracted with 30 mL of methylene chloride. The organic extracts were combined, washed with water, dried over magnesium sulfate, and concentrated in vacuo. The quinone was diluted with 19 mL of methylene chloride and transfered to a dry two-neck flask under positive argon pressure. To this solution was added 1-ethoxy-1-(tert-butyl-dimethylsilyl)-oxy-1,3-butadiene (1.12 g, 4.9 mmole) in 1 mL of methylene chloride at -78°C. The reaction mixture was stirred 15 minutes at -78°C , warmed slowly to ambient temperature, and then recooled to 0°C. The resulting pale yellow solution was

treated sequentially with 10 mL of acetonitrile, 5 mL of a pH = 7.5 phosphate buffer, and tetra-n-butylammonium flouride (4.8 mL of a 1.0 M solution in THF). The resulting dark brown solution was warmed to ambient temperature, acidified with 2 N HCl, and poured into 100 mL of brine. The aqueous phase was extracted with three 40 mL portions of diethyl ether, the organic extracts combined, washed with brine, and dried over magnesium sulfate. The solvents were removed in vacuo and the residue flash chromatographed on silica gel eluting with 2.7:1 hexanes/ethyl acetate to afford 613 mg (77%) of 77, yellow needles from ethyl acetate/hexanes: mp 103-104.5°C; 300 MHz ^{1}H NMR ($CDCl_3$) δ 1.27 (t, 3 H, J = 6.9 Hz), 2.65 (s, 3 H), 2.68 (dd, 1 H, J = 15.6 and 6.3 Hz), 2.87 (dd, 1 H, J = 15.6 and 7.2 Hz), 3.23 (dd, 1 H, J = 16.8 and 7.2 Hz), 3.69 (dd, 1 H, J = 16.8 and 9.6 Hz), 4.01 (s, 3 H), 4.19 (q, 2 H, J = 6.9 Hz), 5.24 (m, 1 H), 6.75 (d, 1 H, J = 7.5 Hz), 7.30-7.50 (m, 2 H), 11.35 (s, 1 H); IR (film) 3005, 1730, 1610, 1390, 1310, 1220, 1150, 1080 cm^{-1}; ^{13}C NMR 14.37, 32.50, 38.38, 41.09, 56.22, 60.64, 78.87, 105.40, 114.75, 115.08, 116.26, 118.56, 124.94, 128.62, 146.79, 154.03, 157.72, 170.40, 201.11 ppm; MS m/e 344, 270, 257, 241; high resolution mass spectrum for $C_{19}H_{20}O_6$ requires 344.12599, determined 344.1259; Anal. Calcd: C, 66.28; H, 5.81. Found: C, 66.31; H, 5.87.

trans-Ethyl[1-Hydroxy-9-methoxy-1-methyl-5,10-dioxo-3,4,5,10-tetrahydronaphtho[2,3-c]pyran-3-yl]acetate (78)

To a solution of 77 (613 mg, 1.78 mmole) in 40 mL of acetonitrile at ambient temperature was added ceric ammonium nitrate (2.36 g, 4.30 mmole) in 8.5 mL of water. The reaction mixture was stirred 30 minutes at ambient temperature, poured into 50 mL of water containing 5 mL of a pH = 7.5 phosphate buffer, and the layers separated. The aqueous phase was extracted twice with 30 mL portions of methylene chloride, the organic extracts combined, washed with water, and dried over magnesium sulfate. The solvents were removed in vacuo and the residue crystallized from methylene chloride/hexanes to afford 553 mg (91%) of 78 as yellow needles: mp 153-154°C; 300 MHz ^{1}H NMR ($CDCl_3$) δ 1.29 (t, 3 H, J = 7.2 Hz), 1.73 (s, 3 H), 2.28 (dd, 1 H, J = 18.7 and 11.1 Hz), 2.64 (dd, 1 H, J = 15.6 and 6.6 Hz), 2.76 (dd, 1 H, J = 15.6 and 6.6 Hz), 2.88 (dd, J = 18.7 and 2.7 Hz), 3.87 (bs, 1 H), 4.02 (s, 3 H), 4.19 (q, 2 H, J = 7.2 Hz), 4.48 (m, 1 H), 7.32 (dd, 1 H, J = 8.1 and 0.9 Hz), 7.64-7.80 (m, 2 H); IR ($CHCl_3$) 3600-3400, 3010, 1730, 1655, 1585, 1270 cm^{-1}; ^{13}C NMR 14.02, 27.64, 28.23, 40.09, 56.71, 60.69, 65.00, 94.30, 118.34, 119.06, 120.01, 133.97, 135.27, 140.35, 146.33, 159.84, 170.19, 182.02, 182.18 ppm; MS m/e 342, 296, 268, 244, 229, 201; high resolution mass spectrum for $C_{19}H_{20}O_7$ requires 360.12091, determined 360.12032; Anal. Calcd: C, 63.33; H, 5.56. Found: C, 63.16; H, 5.62.

cis-Ethyl[9-Methoxy-1-methyl-5,10-dioxo-3,4,5,10-tetrahydro-1H-naphtho[2,3-c]pyran-3-yl]acetate (79)

To a solution of 78 (102 mg, 0.30 mmole) in 15 mL of methylene chloride at -78°C was added trifluoroacetic acid (0.14 mL, 1.8 mmole) and the resulting slurry stirred at -78°C for 15 minutes. To the slurry was added triethylsilane (0.29 mL, 1.8 mmole) at -78°C. The reaction mixture was slowly warmed to ambient temperature over three hours. The resulting yellow solution was concentrated in vacuo and the residue crystallized from diethyl ether/hexanes to afford 93 mg (95%) of 79 as yellow needles: mp 118-119°C, lit. (35) 113-115°C; 300 MHz ^{1}H NMR ($CDCl_3$) δ 1.29 (t, 3 H, J = 7.2 Hz), 1.52 (d, 3 H, J = 6.6 Hz), 2.28 (ddd, 1 H, J = 18.1, 10.5, and 3.7 Hz), 2.60 (dd, 1 H, J = 15.6 and 7.5 Hz), 2.70 (dd, 1 H, J = 15.6 and 7.5 Hz), 2.83 (apparent dt, 1 H, J = 18.1, 2.5, and 2.5 Hz), 3.93 (m, 1 H), 4.00 (s, 3 H), 4.19 (q, 2 H, J = 7.2 Hz), 4.87 (m, 1 H), 7.28 (bd, 1 H, J = 8.4 Hz), 7.64 (t, 1 H, J = 7.8 Hz), 7.73 (dd, 1 H, J = 7.8 and 0.9 Hz); IR (film) 2980, 1730, 1660, 1585, 1270 cm^{-1}; MS m/e 344, 298, 270, 257, 240; high resolution mass spectrum for $C_{19}H_{20}O_6$ requires 344.12599, determined 344.1255; Anal. Calcd: C, 66.28; H, 5.81. Found: C, 66.56; H, 5.85.

cis-Ethyl[9-Hydroxy-1-methyl-5,10-dioxo-3,4,5,10-tetrahydro-1H-naphtho[2,3-c]pyran-3-yl]acetate (81)

To a solution of 79 (58.0 mg, 0.168 mmole) in 12.5 mL of methylene chloride at ambient temperature was added aluminum

trichloride (106 mg, 0.79 mmole) and stirred at ambient temperature for one hour. The reaction mixture was decomposed with 10 mL of water, transferred to a separatory funnel, and 50 mL of water added. The layers were separated and the aqueous layer was extracted five times with 10 mL portions of methylene chloride. The organic extracts were combined, washed with water and brine, and dried over magnesium sulfate. The solvents were removed in vacuo and the residue chromatographed on silica gel eluting with methylene chloride to afford 52.3 mg (94%) of 81 as a bright yellow viscous oil: 300 MHz ^{1}H NMR ($CDCl_3$) δ 1.26 (t, 3 H, J = 7.2 Hz), 1.52 (d, 3 H, J = 6.6 Hz), 2.29 (ddd, 1 H, J = 18.6, 10.4, and 3.9 Hz), 2.58 (dd, 1 H, J = 15.8 and 5.6 Hz), 2.67 (dd, 1 H, J = 15.8 and 7.5 Hz), 2.80 (apparent dt, 1 H, J = 18.6, 2.5, and 2.5 Hz), 3.90 (m, 1 H), 4.16 (q, 2 H, J = 7.2 Hz), 4.82 (m, 1 H), 7.18 (m, 1 H), 7.50-7.60 (m, 2 H), 11.93 (s, 1 H); IR ($CDCl_3$) 2980, 1730, 1660, 1635, 1610, 1455, 1270, 1240 cm^{-1}; ^{13}C NMR 14.29, 21.01, 28.69, 40.61, 60.72, 69.22, 69.99, 115.03, 119.03, 124.44, 131.79, 136.16, 143.49, 146.38, 161.48, 170.51, 182.86, 189.00 ppm.

Epinanaomycin (82)

To a solution of 81 (13.0 mg, 0.0393 mmole) in absolute ethanol was added potassium hydroxide (20 mL of a 0.10 N aqueous solution) and the mixture stirred at ambient temperature 90 minutes. The mixture was carefully acidified

with 2 N HCl and transferred to a separatory funnel. The aqueous phase was extracted four times with 10 mL portions of methylene chloride. The organic extracts were combined, washed with brine, and dried over magnesium sulfate. The solvents were removed in vacuo and the residue crystallized from methylene chloride/hexanes to afford 9.8 mg (82%) of 82 : mp 176-184°C dec, lit. (47) 175-187°C dec, lit. (45) 168-170°C; 300 MHz ^{1}H NMR ($CDCl_3$) δ 1.58 (d, 3 H, J = 6.6 Hz), 2.36 (ddd, 1 H, J = 18.6, 10.3, and 3.9 Hz), 2.64-2.83 (m, 2 H), 2.88 (apparent dt, 1 H, J = 18.6, 2.5, and 2.5 Hz), 3.87-4.02 (m, 1 H), 4.84-4.96 (m, 1 H), 7.22-7.30 (m, 1 H), 7.56-7.68 (m, 2 H), 11.98 (s, 1 H); IR ($CDCl_3$) 2920, 1710, 1660, 1635, 1610, 1455, 1275, 1240 cm^{-1}; MS m/e 302, 284, 242, 214; high resolution mass spectrum for $C_{16}H_{14}O_6$ requires 302.07894, determined 302.07894.

1,4-Dihydroxy-8-methoxy-2(1-oxobutyl)naphthalene (83)

To a solution of phthalide 74 (1.10 g, 5.81 mmole) and propyl vinyl ketone (665 mg, 6.10 mmole, approximately 90% pure) in 29 mL of dimethylsulfoxide at ambient temperature was added potassium tert-butoxide (1.01 g, 9.0 mmole). After stirring 90 minutes at ambient temperature an equal portion of potasium tert-butoxide was added and stirring continued for 90 min. The deep purple solution was diluted with 20 mL of diethyl ether and acidified with 2 N HCl. The resulting yellow solution was poured into 300 mL of ice water and

extracted several times with 1:1 ethyl acetate/diethyl ether. The organic extracts were combined, washed with brine, and dried. The drying agent was removed by filtration and the solvents removed in vacuo to provide a yellow-brown solid, which was triturated with diethyl ether/hexanes to afford 889 mg (59%) of 83 as a yellow-orange solid: mp softens at 160°C, melts at 186-188°C; 300 MHz ^{1}H NMR (CD_3COCD_3) δ 1.00 (t, 3 H, J = 7.5 Hz), 1.75 (m, 4 H), 3.02 (t, 2 H, J = 7.2 Hz), 4.01 (s, 3 H), 7.01 (d, 1 H, J = 8.1 Hz), 7.21 (s, 1 H), 7.52 (t, 1 H, J = 8.1 Hz), 7.77 (d, 1 H, J = 8.1 Hz), 9.45 (s, 1 H), 13.08 (s, 1 H); IR ($CHCl_3$) 3600, 3400-3200, 3005, 1625, 1610, 1390, 1220 CM^{-1}; ^{13}C NMR 13.50, 18.35, 41.20, 56.31, 114.72, 114.85, 116.86, 129.10, 132.10, 132.29, 144.91 144.79, 156.25, 159.50, 204.68 ppm; MS m/e 260, 217; high resolution mass spectrum for $C_{15}H_{16}O_4$ requires 260.10486, determined 260.10481.

(E/Z)-1-Methoxy-1-(tert-butyldimethylsilyl)oxy-1,3-butadiene 68b

To a solution of diisopropylamine (5.76 mL, 41.3 mmole) in 80 mL of THF at -10°C was slowly added n-butyllithium (16.26 mL of a commercial 2.52 M solution, 41.0 mmole) over 5 min. The amide base thus formed was cooled to -78°C and 7.8 mL of hexamethylphosphoric triamide added to afford a white suspension. After stirring for 30 minutes at -78°C, methyl crotonate (4.24 mL, 40 mmole) was added via a double-ended

needle from a precooled (-78°C) 2.6 M solution in THF under positive argon pressure over 10 minutes. The resulting pale yellow solution was stirred at -78°C for 30 minutes and treated with tert-butyldimethylsilyl chloride (6.38 g, 42.4 mmole) in 10 mL of THF and warmed slowly to ambient temperature. After stirring for 3 h at ambient temperature, the solvents were removed in vacuo and the residue treated with 50 mL of pentanes and filtered. The clear nearly colorless filtrate was concentrated in vacuo and distilled at reduced pressure to afford 4.5 g (53%) of 68b as a clear colorless liquid: bp 59-60°C at 0.70 mmHg; 300 MHz ^{1}H NMR ($CDCl_3$) δ 0.18 (bs, 6 H), 0.96 (bs, 9 H), 3.55 (s, 3 H), 4.4-4.65 (m, 2 H), 4.80-4.91 (m, 1 H), 6.45-6.62 (m, 1 H). ^{13}C NMR -4.15, -3.6 (minor), 18.21 (minor), 25.69, 54.83, 80.54, 80.63, 106.83, 132.47, 158.79 ppm.

Methyl[6-Hydroxy-7-methoxy-5-(1-oxobutyl)-3,4-dihydronaphtha[1,2-b]furan-3-yl]acetate (84)

To a solution of 83 (830 mg, 3.19 mmole) in 40 mL of acetonitrile and 10 mL of THF at ambient temperature was added ceric ammonium nitrate (4.02 g, 7.34 mmole) in 5 mL of water. After stirring 30 minutes at ambient temperature, the bright yellow solution was diluted with 40 mL of methylene chloride and poured into 125 mL of water containing 10 mL of a 1 M pH = 7.2 phosphate buffer. The layers were separated and the aqueous phase extracted with two 40 mL portions of methylene

chloride. The organic extracts were combined, washed with water, dried over magnesium sulfate, and concentrated *in vacuo*. The quinone was dissolved in 35 mL of methylene chloride and transferred to a dry 100 mL two-neck flask with positive argon pressure. The solution was cooled to -78°C, and the ketene acetal **68b** (0.72 g, 3.34 mmole) in 1 mL of methylene chloride added dropwise over 1 minute. The reaction mixture was stirred at -78°C for 15 minutes, warmed to 0°C, and treated sequentially with 15 mL of acetonitrile, 10 mL of a dilute pH = 7.5 phosphate buffer, and tetra-*n*-butylammonium fluoride (7.5 mL of a 1.0 *M* solution in THF). After warming to ambient temperature, the reaction mixture was acidified with 2 *N* HCl and poured into 150 mL of brine. The aqueous solution was extracted four times with 30 mL portions of diethyl ether, the organic extracts combined, washed with brine, and dried. The drying agent was filtered and the solvents were removed *in vacuo* to provide a yellow-orange solid. Flash chromatography on silica gel eluting with 3:1 hexanes/ethyl acetate afforded 0.793 g (70%) of **84** as a yellow solid, yellow-green needles from diethyl ether/hexanes: mp 99.5-100.5°C; 300 MHz ^{1}H NMR (CD_3COCD_3) δ 0.96 (t, 3 H, J = 7.5 Hz), 1.62-1.80 (m, 4 H), 2.77 (dd, 1 H, J = 15.6 and 6.3 Hz), 2.86 (dd, 1 H, J = 15.6 and 7.2 Hz), 3.01 (t, 2 H, J = 7.2 Hz), 3.20 (dd, 1 H, J = 16.8 and 7.2 Hz), 3.64 (dd, 1 H, J = 16.8 and 9.3 Hz), 5.23 (m, 1 H), 6.86-6.98 (m, 1 H),

7.31-7.45 (m, 2 H), 10.65 (s, 1 H); IR ($CHCl_3$) 3360, 3005, 1732, 1630, 1405 cm^{-1}; ^{13}C NMR 12.58, 16.79, 36.51, 39.47, 44.93, 50.09, 55.15, 78.18, 104.48, 113.76, 116.75, 118.28, 123.12, 127.16, 145.83, 149.97, 150.38, 156.56, 169.43, 202.13 ppm; MS m/e 358, 315, 298, 285, 252, 241; high resolution mass spectrum for $C_{20}H_{22}O_6$ requires 358.14164, determined 358.1410; Anal. Calcd: C 67.03; H, 6.14. Found: C, 66.86; H, 6.30.

trans-Methyl[1-Hydroxy-9-methoxy-5,10-dioxo-1-N-propyl-3,4,5,10-tetrahydronaphtho[2,3-c]pyran-3-yl]acetate (85)

To a suspension of 84 (474 mg, 1.32 mmole) in 30 mL of acetonitrile at ambient temperature was added ceric ammonium nitrate (1.66 g, 3.03 mmole) in 6 mL of water. After stirring at ambient temperature for 30 minutes, the solution was poured into 100 mL of a dilute pH = 7.5 phosphate buffer. The aqueous solution was extracted three times with 20 mL portions of methylene chloride, the organic extracts combined, and dried over magnesium sulfate. The drying agent was filtered and the solvents removed in vacuo to provide a yellow foamy solid which was crystallized from methylene chloride/hexanes to afford 470 mg (94%) of 85 as yellow needles: mp 133.5-135°C; 300 MHz ^1H NMR ($CDCl_3$) δ .84 (t, 3 H, J = 7.2 Hz), 0.9-1.50 (m, 4 H), 1.86-2.01 (m, 1 H), 2.03-2.20 (m, 1 H), 2.25 (dd, 1 H, J = 18.6 and 10.8 Hz), 2.66 (dd, 1 H, J = 15.8 and 6.5 Hz), 2.78 (dd, 1 H, J = 15.8 and 6.5 Hz), 2.87 (dd, J = 18.6 and 2.7 Hz), 3.73 (s, 3 H), 4.02 (s, 3 H),

4.38-4.47 (m, 1 H), 7.28-7.36 (m, 1 H), 7.63-7.74 (m, 2 H); IR ($CHCl_3$) 2970, 1735, 1650, 1585, 1270, 1205 cm^{-1}; ^{13}C NMR 13.82, 16.92, 27.56, 39.71, 42.50, 51.44, 51.52, 56.28, 64.27, 96.15, 118.03, 118.80, 133.89, 134.84, 141.01, 144.48, 159.54, 170.55, 183.52, 183.92 ppm; MS m/e 356, 324, 313, 296, 272, 257, 229, 201; high resolution mass spectrum for $C_{20}H_{22}O_7$ requires 374.13656, determined 374.1367.

cis-Methyl[9-Methoxy-9,10-dioxo-1-N-propyl-3,4,5,10-tetrahydro-1H-naphtho[2,3-c]pyran-3-yl]acetate (86)

To a solution of 85 (470 mg, 1.32 mmole) in 30 mL of methylene chloride at -78°C was added trifluoroacetic acid (0.61 mL, 7.92 mmole) and the resulting slurry stirred at -78°C for 10 minutes. To the slurry was added triethylsilane (1.26 mL, 7.92 mmole) and the reaction mixture warmed to ambient temperature over 1 hour. The volatiles were removed in vacuo and the residue flash chromatographed on silica gel eluting with 2:1:0.4 hexanes/ethyl acetate/methylene chloride to afford 398 mg (84%) of 86, yellow needles from diethyl ether/hexanes: mp 148-149.5°C, lit. (44) 144-148.5°C; 300 MHz ^1H NMR ($CDCl_3$) δ 0.90 (t, 3 H, J = 7.2 Hz), 1.30-1.60 (m, 2 H), 1.62-1.82 (m, 1 H), 1.93-2.08 (m, 1 H), 2.24 (ddd, J = 18.0, 10.5, and 3.9 Hz), 2.61 (dd, 1 H, J = 15.6 and 5.6 Hz), 2.70 (dd, 1 H, J = 15.6 and 7.5 Hz), 2.83 (apparent dt, 1 H, J = 18.0, 2.4, and 2.4 Hz), 3.72 (s, 3 H), 3.82-3.94 (m, 1 H), 3.99 (s, 3 H), 4.76-4.85 (m, 1 H), 7.26 (dd, 1 H, J = 8.1 and

0.6 Hz), 7.62 (t, 1 H, J = 8.1 Hz), 7.72 (dd, 1 H, J = 7.8 and 0.9 Hz); IR (film) 2960, 1735, 1658, 1585, 1270, 730 cm^{-1}; ^{13}C NMR 13.87, 18.55, 28.07, 36.26, 40.60, 51.65, 56.56, 69.21, 73.91, 118.02, 119.09, 120.57, 134.20, 134.48, 139.98, 148.11, 159.60, 171.02, 183.34, 183.54 ppm; Anal. Calcd for $C_{20}H_{22}O_6$: C, 67.03; H, 6.14. Found: C, 66.91; H, 6.37.

3α,4α-(Isopropylidenedioxy)-6β-3,4,5,6-tetrahydropyran-2-one (91)

To a solution of 90 (7.38 g, 65.9 mmole) in 175 mL of 4:3 water/THF at ambient temperature was added potassium chlorate (9.7 g, 71.7 mmole) and osmium tetroxide (22 mL of an aqueous solution containing 5 mg/mL) and the mixture stirred at 45°C for 12 hours. The solvents were removed in vacuo and the residue coevaporated three times with 100 mL portions of 1:1 benzene/ethanol. The residue was dried under high vacuum for three hours and the solid residue extracted with three 50 mL portions of 4:1 ethyl acetate/acetone. The organic extracts were dried over magnesium sulfate, the drying agent filtered, and the solvents removed in vacuo to afford the diol as a clear syrup. The crude diol was dissolved in 400 mL of absolute acetone and treated with 0.8 mL of concentrated sulfuric acid. The clear solution was stirred at ambient temperature for 16 hours, neutralized with saturated aqueous sodium bicarbonate solution, and the solvents removed in vacuo. The residue was flash chromatographed on silica gel

eluting with 2.5:1 hexanes/ethyl acetate to afford 6.28 g (51%) of 91 as a clear liquid: 300 MHz ^{1}H NMR ($CDCl_3$) δ 1.38 (s, 3 H), 1.39 (d, 3 H, J = 6.3 Hz), 1.51 (s, 3 H), 1.71-1.83 (m, 1 H), 2.01-2.08 (m, 1 H), 4.57 (d, 1 H, J = 6.9 Hz), 4.62-4.68 (m, 1 H), 4.69-4.81 (m, 1 H); IR (neat) 2995, 2940, 1750, 1380, 1260, 1210, 1080 cm^{-1}; ^{13}C NMR 20.64, 23.87, 25.87, 35.42, 71.30, 71.82, 72.46, 110.38, 168.00 ppm.

tert-Butyldimethylsilyloxyl[4,6-Dideoxy-2,3-O-isopropylidene-5-O-(tert-butyldimethylsilyl)gulonate (93)

To a solution of potassium hydroxide (0.40 g, 6.2 mmole) in 20 mL of 95% aqueous methanol at ambient temperature was added 91 (895 mg, 4.80 mmole) in 10 mL of 95% methanol. The solution was stirred at ambient temperature for 16 hours and concentrated to dryness in vacuo.

To a suspension of the crude salt in 20 mL of dimethylformamide at ambient temperature was added imidazole (2.5 g, 38.4 mmole) and tert-butyldimethylsilyl chloride (2.88 g, 19.2 mmole). The resulting clear solution was stirred at ambient temperature for 16 hours, poured into 100 mL of brine, and extracted with three 50 mL portions of 1:1 hexanes/diethyl ether. The organic extracts were combined, washed with 50 mL of cold 1 N HCl and brine, and dried. The drying agent was filtered and the solvents removed in vacuo to afford 2.22 g (107%) of 93 as a clear oil contaminated with an undetermined silicon containing by-product: 300 MHz ^{1}H NMR

($CDCl_3$) δ 0.08 (s, 3 H), 0.10 (s, 3 H), 0.25 (s, 3 H), 0.31 (s, 3 H), 0.85 (s, 9 H), 0.88 (s, 9 H), 1.16 (d, 3 H, J = 6.0 Hz), 1.34 (s, 3 H), 1.58 (s, 3 H), 1.60-1.66 (m, 1 H), 1.68-1.79 (m, 1 H), 4.00 (m, 1 H), 4.35-4.44 (m, 1 H), 4.49 (d, 1 H, J = 6.9 Hz).

4,6-Dideoxy-2,3-O-isopropylidene-5-O-tert-butyldimethylsilylgulonaldehyde (94)

To a suspension of lithium aluminium hydride (390 mg, 10.2 mmole) in 30 mL of THF at 0°C was added the crude ester 93 from above in 4 mL of THF dropwise via syringe. The suspension was slowly warmed to ambient temperature and stirred two hours. With vigorous stirring, the suspension was treated with saturated sodium sulfate solution until a fine microcrystalline precipitate formed (ca. 2 mL). The precipitated salts were filtered and the filtrate concentrated in vacuo to afford 1.47 g of the primary alcohol of sufficient purity for further transformations: 300 MHz ^1H NMR ($CDCl_3$) δ 0.12 (bs, 6 H), 0.88 (s, 9 H), 1.18 (d, 3 H, J = 6.3 Hz), 1.36 (s, 3 H), 1.45 (s, 3 H), 1.51-1.62 (m, 1 H), 1.74-1.86 (m, 1 H), 2.06 (t, 1 H, J = 6.6 Hz), 3.62 (t, 2 H, J = 6.6 Hz), 3.94-4.06 (m, 1 H), 4.12-4.19 (m, 1 H), 4.24-4.37 (m, 1 H).

To a solution of the crude alcohol from above in 30 mL of methylene chloride at ambient temperature was added sodium acetate (2.0 g, 23.8 mmole), followed by pyridinium chlorochromate (3.10 g, 14.4 mmole). The orange-brown

solution was stirred three hours and diluted with 50 mL of diethyl ether. The brown suspension was filtered through a short plug of Florosil and the filtrate was concentrated *in vacuo* to provide 0.96 g (66%) of **94**. Aldehyde **94** is unstable and darkens on standing at 0°C: 300 MHz ^{1}H NMR ($CDCl_3$) δ 0.05 (s, 3 H), 0.08 (s, 3 H), 0.98 (s, 9 H), 1.15 (d, 3 H, J = 6.3 Hz), 1.40 (s, 3 H), 1.57 (s, 3 H), 1.60-1.78 (m, 2 H), 3.97 (apparent ABq, 1 H, J = 12.3 and 6.0 Hz), 4.22 (dd, 1 H, J = 6.9 and 3.6 Hz), 4.42-4.50 (m, 1 H), 9.62 (d, 1 H, J = 3.6 Hz).

4R*,5R*,7R*-3,4-Isopropylidenedioxy-7-(*tert*-butyldimethylsilyloxy)-oct-1-ene-3-one (**95**)

To a solution of aldehyde **94** (0.96 g, 3.17 mmole) in 20 mL of diethyl ether at 0°C was added vinyl magnesium bromide (3.5 mL of a commercial 1.0 *M* solution in THF). The grey-brown solution was warmed to ambient temperature and quenched with 3 mL of saturated aqueous ammonium chloride solution. The two-phase mixture was transferred to a separatory funnel and extracted twice with 15 mL portions of ether. The ethereal layers were combined, washed with brine, and dried. The solvents were removed *in vacuo* and the residue was dissolved in 3 mL of diethyl ether. To this stirred solution was added the Jones' reagent (1.6 mL of a solution prepared by the method of Brown et al. (77)) and the mixture vigorously stirred for 30 minutes at ambient temperature. The two-phase

mixture was diluted with 10 mL of 1:1 pentanes/diethyl ether and the phases separated. The organic phase was washed with brine, dried, and filtered. The filtrate was concentrated *in vacuo* and the residue flash chromatographed on silica gel eluting with 6:1 hexanes/diethyl ether to afford 240 mg (23%) of **95** as a clear oil which was used immediately: 300 MHz ^{1}H NMR ($CDCl_3$) δ 0.28 (s, 3 H), 0.03 (s, 3 H), 0.86 (s, 9 H), 1.13 (d, 3 H, J = 6.6 Hz), 1.37 (s, 3 H), 1.41-49 (m, 1 H), 1.54-1.65 (m, 4 H), 3.93 (m, 1 H), 4.45-4.54 (m, 1 H), 4.59 (d, 1 H, J = 7.8 Hz), 5.74 (dd, 1 H, J = 10.5 and 1.8 Hz), 6.34 (dd, 1 H, J = 17.4 and 1.8 Hz), 6.77 (dd, 1 H, J = 17.4 and 10.5 Hz).

1,4-Dihydroxy-2-[2R*,3R*,5R*-2,3-isopropylidenedioxy-1-oxo-5-(*tert*-butyldimethylsilyloxy)hexyl]-8-methoxynaphthalene (**96**)

To a solution of phthalide **74** (133 mg, .708 mmole) in 10 mL of dimethylsulfoxide at ambient temperature was added the enone **95** (240 mg, 0.73 mmole) followed by potassium *tert*-butoxide (122 mg, 1.10 mmole). The reaction mixture was stirred at ambient temperature for 90 minutes an additional portion of base (122 mg, 1.10 mmole) was added and the reaction mixture stirred 90 minutes at ambient temperature. The solution was carefully neutralized with 1 *N* HCl to pH = 5 and diluted with 20 mL of diethyl ether. The resulting yellow solution was poured into 20 mL of water and the aqueous phase extracted with 20 mL of diethyl ether. The organic extracts

were combined, washed with brine, and dried. The solvents were decanted from the drying agent and removed in vacuo. Flash chromatography of the residue on silica gel eluting with 4:1 hexanes/ethyl acetate afforded 51 mg (15%) of 96 as a yellow oil: 300 MHz ^{1}H NMR ($CDCl_3$) δ 0.19 (s, 3 H), 0.21 (s, 3 H), 1.02 (s, 9 H), 1.37 (d, 3 H, J = 6.0 Hz), 1.59 (s, 3 H), 1.69 (s, 3 H), 1.95-2.05 (m, 1 H), 2.14-2.23 (m, 1 H), 4.22 (s, 3 H), 4.73-4.80 (m, 1 H), 5.24 (d, 1 H, J = 6.3 Hz), 7.10 (d, 1 H, J = 7.8 Hz), 7.44 (s, 1 H), 7.71 (t, 1 H, J = 7.8 Hz), 7.96 (d, 1 H, J = 7.8 Hz).

2-[2R*,3R*,5R*-2,3-Isopropylidenedioxy-5-methoxymethyl-1-oxo-hexyl]-1,4,8-trimethoxynaphthalene (99)

To a solution of the bromide 97 (303 mg, 1.19 mmole) in 10 mL of THF at -78°C was added n-butyllithium (0.46 mL of a commercial 2.6 M solution in hexanes, mmole). The resulting light yellow solution stirred at -78°C for 20 minutes and 91 (218 mg, 1.17 mmole) in 1 mL of THF was added dropwise via syringe. The light yellow solution was stirred at -78°C for one hour and then quenched with saturated ammonium chloride solution (ca. 5 mL). The resulting suspension was warmed to ambient temperature and transferred to a separatory funnel containing 15 mL of brine and 5 mL of diethyl ether. The layers were partitioned and the aqueous layer extracted twice with 10 mL portions of 1:1 pentanes/diethyl ether. The organic extracts were combined, washed with brine, and dried.

The solvents were removed in vacuo to provide a yellow viscous oil, which was dissolved in 5 mL of methylene chloride and cooled to 0°C. To this solution was added diisopropylethylamine (1.9 mL, 11.2 mmole) followed by chloromethyl methyl ether (0.77 mL, 5.6 mmole) and the resulting dark yellow solution warmed to ambient temperature. After stirring 48 hours at ambient temperature, the mixture was diluted with 50 mL of 1:1 pentanes/diethyl ether and transferred to a separatory funnel containing 50 mL of brine. The organic phase was separated and washed successively with 2 N HCl, water, 5% aqueous sodium bicarbonate, and brine. The extracts were dried, filtered from the drying agent, and concentrated in vacuo to provide a yellow oil. Flash chromatography of the residue on silica gel eluting with hexanes/ethyl acetate afforded 210 mg (45%) of 99 as a pale yellow oil: 300 MHz ^{1}H NMR ($CDCl_3$) δ 1.04 (d, 3 H, J = 6.3 Hz), 1.23-1.40 (m, 1 H), 1.41 (s, 3 H), 1.64 (s, 3 H), 1.69-1.83 (m, 1 H), 3.22 (s, 3 H), 3.68-3.79 (m, 1 H), 3.80 (s, 3 H), 3.96 (s, 3 H), 4.01 (s, 3 H), 4.46-4.57 (m, 2 H), 5.85 (d, 1 H, J = 6.6 Hz), 6.93 (s, 1 H), 6.96 (d, 1 H, J = 8.1 Hz), 7.48 (t, 1 H, J = 8.1 Hz), 7.85 (dd, 1 H, J = 7.8 and 0.9 Hz); IR (film) 2930, 1680, 1595, 1370, 1265, 1070, 815 cm^{-1}.

3,5-Dideoxy-2,4-O-benzylidene-D-xylose,dibutylthio Acetal (105)

To a solution of 104 (0.62 g, 1.55 mmole) in 15 mL of pyridine was added tosyl chloride (1.45 g, 4.65 mmole) and the pale yellow solution stirred at ambient temperature for 48 h. The solution was poured into 100 mL of water and extracted with three 20 mL portions of diethyl ether. The organic extracts were combined, washed with 2 N HCl and brine, and dried. The solvents were removed in vacuo and the residue chromatographed on silica gel eluting with 3:1 hexanes/diethyl ether to afford 760 mg (69%) of the bistosylate as a light yellow semi-solid: 300 MHz ^{1}H NMR ($CDCl_3$) δ 0.85 (t, 3 H, J = 6.9 Hz), 0.96 (t, 3 H, J = 6.9 Hz), 1.22-1.69 (m, 8 H), 2.41 (s, 3 H), 2.43 (s, 3 H), 2.54 (t, 2 H, J = 6.9 Hz), 2.68 (t, 2 H, J = 6.9 Hz), 3.85 (ABq, 2 H, J_{gem} = 12.8 Hz), 4.04-4.29 (m, 3 H), 5.32 (s, 1 H), 5.55 (s, 1 H), 7.20-7.45 (m, 9 H), 7.70-7.86 (m, 4 H); IR (film) 3040, 2960, 1595, 1360, 1175, 730 cm^{-1}.

To a solution of the bistosylate (200 mg, 0.282 mmole) in 10 mL of hexamethylphosphoric triamide at ambient temperature was added sodium borohydride (55 mg, 1.41 mmole) and the mixture warmed to 100°C. After stirring 36 hours at 100°C, the reaction mixture was cooled and poured into 50 mL of brine. The aqueous phase was extracted three times with 20 mL portions of diethyl ether, the organic extracts combined, washed several times with brine, and dried. Flash

chromatography on silica gel eluting with 10:1 hexanes/diethyl ether afforded 40 mg (39%) of 105 as a clear oil: 300 MHz ^{1}H NMR ($CDCl_3$) δ 0.91 (t, 6 H, J = 6.6 Hz), 1.30-1.50 (m, 7 H), 1.5-1.65 (m, 4 H), 1.65-1.88 (m, 2 H), 2.63-2.85 (m, 4 H), 3.89 (d, 1 H, J = 6.9 Hz), 3.92-4.00 (m, 1 H), 4.03-4.12 (m, 1 H), 5.52 (s, 1 H), 7.29-7.42 (m, 3 H), 7.45-7.52 (m, 2 H); IR (film) 2950, 1450, 1020, 730 cm^{-1}.

3,5-Dideoxy-D-xylose,dibutylthio Acetal (106)

To a solution of 105 (16 mg, 0.043 mmole) in 1 mL of methylene chloride at ambient temperature was added trifluoroacetic acid (100 μL of a 70% aqueous solution) and the mixture stirred vigorously for 90 min. To this two-phase mixture was added 1 mL of saturated sodium bicarbonate solution and the whole transferred to a separatory funnel. The organic layer was separated, the aqueous layer diluted with 10 mL of brine, and extracted with two 10 mL portions of methylene chloride. The organic extracts were combined, washed with brine, and dried. The solvents were removed *in vacuo* and the residue filtered through a short column of silica gel eluting with 4:1 hexanes/ethyl acetate to afford 8.0 mg (66%) of 106 as a clear oil: 300 MHz ^{1}H NMR ($CDCl_3$) δ 0.93 (s, 6 H), 1.22 (d, 3 H, J = 6.3 Hz), 1.34-1.51 (m, 4 H), 1.52-1.71 (m, 6 H), 1.92-2.08 (m, 1 H), 2.56-2.74 (m, 4 H),

3.37 (bs, 1 H), 3.50 (bs, 1 H), 3.72 (d, 1 H, J = 6.6 Hz), 3.79-3.91 (m, 1 H), 3.96-4.11 (m, 1 H); IR 3600-3200, 2960, 1560, 1280, 840 cm^{-1}.

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OVERALL SUMMARY

Part I describes the construction of the major carbon framework of olivin, the aglycone of a number of antitumor antibiotics collectively known as the olivomycins. A palladium(0) mediated cross-coupling of a metallated ethyl vinyl ether unit and an enol triflate derived from a readily available carbohydrate was accomplished. In this first key step, most of the carbon and oxygen atoms of the side chain and A ring of the aglycone were assembled in the form of a diene. The second key step was the Diels-Alder cycloaddition of the complex carbohydrate substituted diene to a highly functionalized naphthoquinone. The resulting cycloadduct, which was formed with complete regiochemical control, has all of the necessary functionality intact for eventual conversion to olivin.

Part II describes a direct and operationally convenient synthesis of the DCB ring subunit of aklavinone, the aglycone of the potent cytostatic agent aclacinomycin A. The synthesis begins with a Diels-Alder reaction between 1-trimethylsilyl-oxy-1,3-butadiene and 2-cyano-5-methoxy-3-phenylthio-1,4-naphthoquinone. Oxidation of the Diels-Alder adduct produced a novel blocked anthraquinone tautomer. The blocked anthraquinone was converted to the DCB subunit of aklavinone by conjugate addition of a mixed ketene acetal, selective mercaptan oxidation, and elimination of benzenesulfenic acid

and hydrocyanic acid. The three rings of the aklavinone precurser were constructed in high yield and with complete stereochemical control. In addition, the novel reactivity patterns of two phenylsulfinyl substituted naphthoquinones were investigated. In the case of 2-allyl-8-methoxy-3-phenylsulfinylnaphthoquinone, a tandem Diels-Alder-sulfoxide elimination-retro-Claisen sequence occurred upon heating with 1-trimethylsilyloxy-1,3-butadiene to produce a anthracene derivative.

Part III describes successful syntheses of nanaomycin A and deoxyfrenolicin, important members of the naphtho[2,3-c]-pyran-5,10-quinone class of antibiotics. In addition, synthetic efforts toward the more complex members, griseusins A and B, are described. A key step in the syntheses of the two former members is a tandem Diels-Alder-retro-Claisen reaction between 3-acyl-5-methoxy-1,4-naphthoquinones and mixed vinyl ketene acetals. The resulting 2,3-dihydro-naphtho[1,2-b]furans are oxidized in high yield to intermediate 3-acyl-2-(2-hydroxyalkyl) substituted naphthoquinones which spontaneously form hemiketals. Finally, the hemiketals were stereospecifically reduced to afford advanced intermediates in previously published syntheses of nanaomycin A and deoxyfrenolicin.

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