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Synthesis of 11-deoxyanthracyclines

Soon Hyung Woo
Iowa State University

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Synthesis of 11-deoxyanthracyclines

by

Soon Hyung Woo

A Dissertation Submitted to the

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For the Graduate College

Iowa State University
Ames, Iowa

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TABLE OF CONTENTS

GENERAL INTRODUCTION

The anthracycline antitumor agents such as adriamycin and daunomycin have been developed over the last 15 years into major chemotherapeutic agents for the treatment of human cancers. Their broad spectrum of antitumor activity, limited to some degree by toxic side effects, has led to vigorous competition by organic chemists to achieve enhanced therapeutic index for these and related anthracycline antibiotics. Recently, a new series of naturally-occurring 11-deoxyanthracyclines were discovered and have proven to possess better therpeutic properties than adriamycin and daunomycin.

This manuscript details the results of a program aimed at developing general synthetic approaches to 11-deoxyanthracyclines. The first part describes the total synthesis of 11-deoxydaunomycinone and its analogs by a tandem Claisen-Diels-Alder strategy. The second part deals with the synthesis of linear polycyclic quinones via the Diels-Alder reaction. The utility of this reaction for the preparation of 11-deoxyanthracyclines is also described.

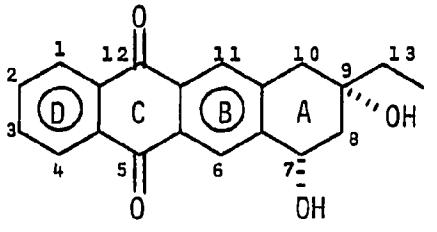
Explanation of Thesis Format

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

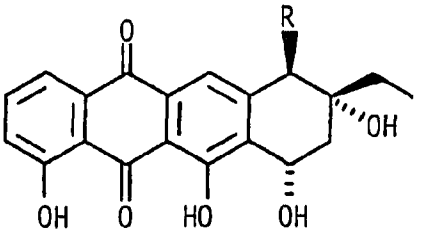
PART I. TOTAL SYNTHESIS OF 11-DEOXYDAUNOMYCINONE AND ANALOGS BY A TANDEM CLAISEN-DIELS-ALDER STRATEGY

HISTORICAL

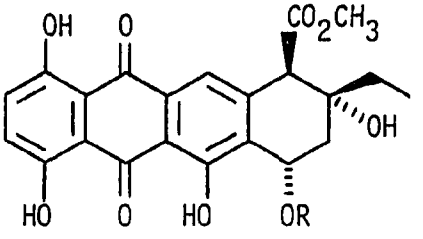
The anthracyclines constitute a growing class of natural antitumor antibiotics isolated from cultures of various Streptomyces spp. The name anthracycline is based on the structural features associated with this family of compounds. They all possess an anthraquinone chromophore within a linear tetracyclic hydrocarbon framework. The basic skeleton and the numbering convention of the anthracyclines are shown below.



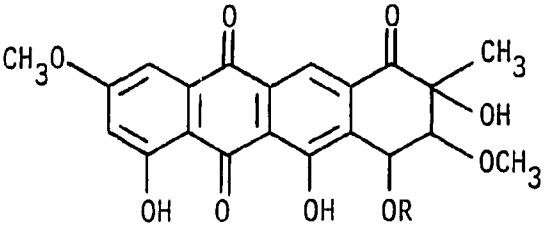
All anthracyclines contain a carbohydrate residue in the form of α-pyranoside linkage which is usually located at the C-7 position of the aglycones, known as anthracyclinones. Within the anthracyclinones, certain families of related compounds have been defined. They are based mainly upon the number and location of phenolic hydroxyl groups on the nucleus. Individual members of each family differ in the number of aliphatic hydroxyl groups and carbomethoxy groups in ring A. Representatives of the anthracyclines and aglycones are shown below, along with structures of some important L-pyranose sugars.



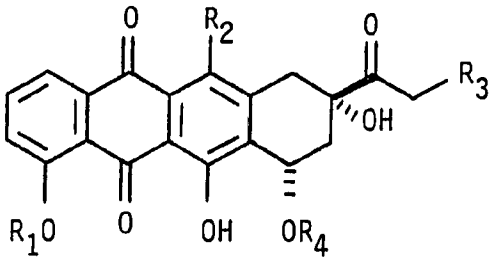
	R
α-Citromycinone	OH
γ-Citromycinone	H



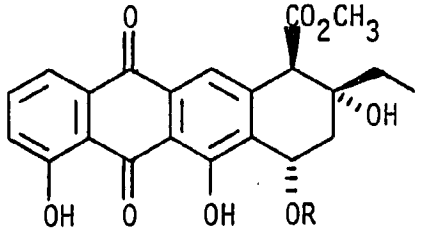
	R
Pyrromycin	Rhodosamine
Cinerubin A	Rhodosamine + 2-deoxy-L-fucose + L-cinerulose



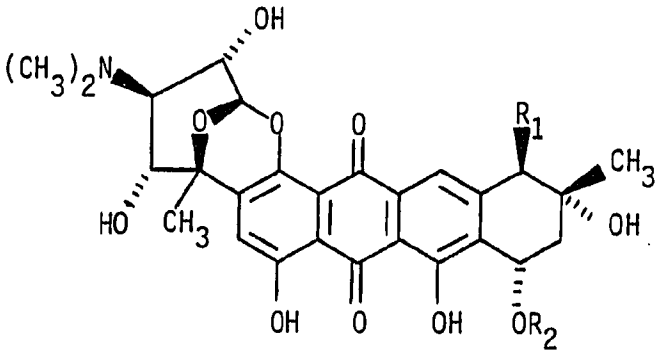
	R
Steffimycin	2-O-Methyl-L-rhamnose
Steffimycin B	2,4-Di-O-methyl-L-rhamnose



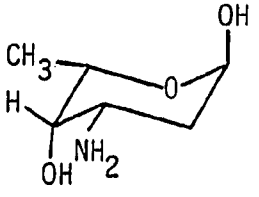
	R_1	R_2	R_3	R_4
Daunomycin	CH_3	OH	H	Daunosamine
11-Deoxydaunomycin	CH_3	H	H	Daunosamine
Adriamycin	CH_3	OH	OH	Daunosamine
11-Deoxyadriamycin	CH_3	H	OH	Daunosamine
Carminomycin	H	OH	H	Daunosamine



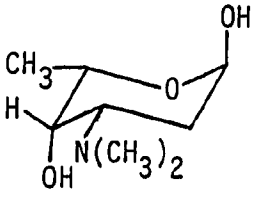
	R
Aklavinone	H
Aclacinomycin A	Rhodosamine + 2-deoxy-L-fucose + L-cinerulose
Aclacinomycin B	Rhodosamine + 2-deoxy-L-fucose + cinerulose B



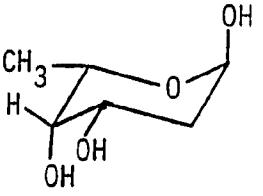
	R_1	R_2
Nogalamycin	CO_2CH_3	Nogalose
Nogamycin	H	Nogalose
7-Con-O-Methynogarol	H	CH_3



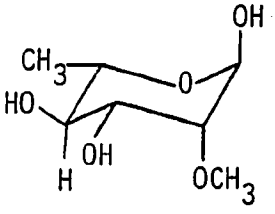
Daunosamine



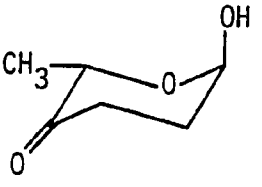
Rhodosamine



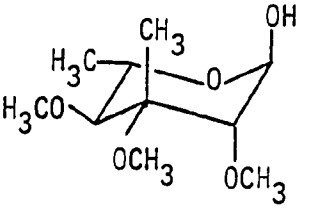
2-Deoxy-L-fucose



2-O-Methyl-L-rhamnose



L-Cinerulose



Nogalose

Since the seminal work in 1963 describing the isolation of daunomycin,[1] the structures of over 40 members of this class of compounds have been elucidated. Among these, daunomycin and adriamycin have been extensively studied clinically and have been accepted as major therapeutic tools in the treatment of human cancers. Daunomycin is particularly effective against mycloblastic and lymphoblastic leukemias,[2] while adriamycin plays a significant role in the treatment of breast and bladder adenocarcinoma, testicular carcinoma, Hodgkin's disease, and acute leukemias.[3] Unfortunately, their extensive use is limited, to some degree, by toxic side effects which include myelo-suppression, stamatitis, alopecia, and cardiac toxicity. Therefore, there has been an intense interest in the search for new anthracyclines with improved chemotherapeutic properties.

Over the last 15 years, several hundred semisynthetic modifications of the natural anthracyclines have been carried out at many academic and industrial laboratories.[4] At the same time, several research groups have undertaken the more elaborate challenge of achieving the total synthesis of daunomycin and related anthracycline antibiotics. In recent years, a new series of naturally-occurring anthracycline antitumor agents having attractive therapeutic indices have been discovered. These "second generation" anthracyclines have a deoxy B-ring as a common structural feature. Among the new agents, 11-deoxydaunomycin and the aclacinomycins are the best known members of this family.

The aclacinomycins, represented by aclacinomycin A, were isolated from Streptomyces Galileus MA 144-M1 by Oki and coworkers in 1975.[5] Aclacinomycin A was found to display strong antineoplastic activity similar to that of adriamycin with 10 to 15 times less cardiotoxicity.[6] Certain side effects attending daunomycin and adriamycin are observed to a much less extent with aclacinomycin A. As a consequence, aclacinomycin A has emerged as a new clinically useful drug.

The biochemical, pharmacodynamic, and chemical aspects of aclacinomycin A and other related anthracycline antibiotics have been studied extensively and are the subjects of several books[7-13] and recent reviews.[14-20]

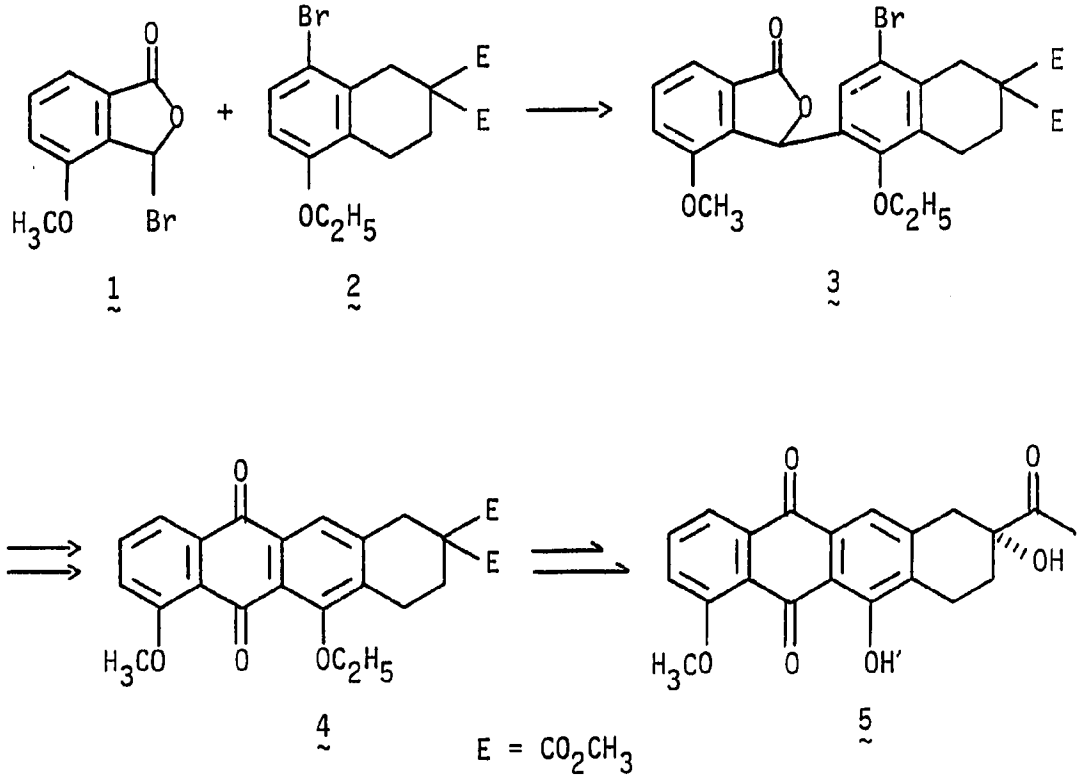
More recently, Arcamone and coworkers[21] announced isolation of 11-deoxydaunomycin, together with 11-deoxyadriamycin and 11-deoxycarminomycin, from a Micromonspora peucetica strain. Biological studies revealed that 11-deoxydaunomycin also has good antitumor activity and much less cardiotoxicity than the parent anthracyclines.[21] The potential advantages associated with these new 11-deoxyanthracyclines have aroused much interest among synthetic organic chemists in developing an efficient route for the synthesis of their aglycones. This historical will summarize the recent synthetic approaches to 11-deoxyanthracyclinones. The emphasis will be placed on general synthetic strategies rather than operational details.

Synthetic Approaches

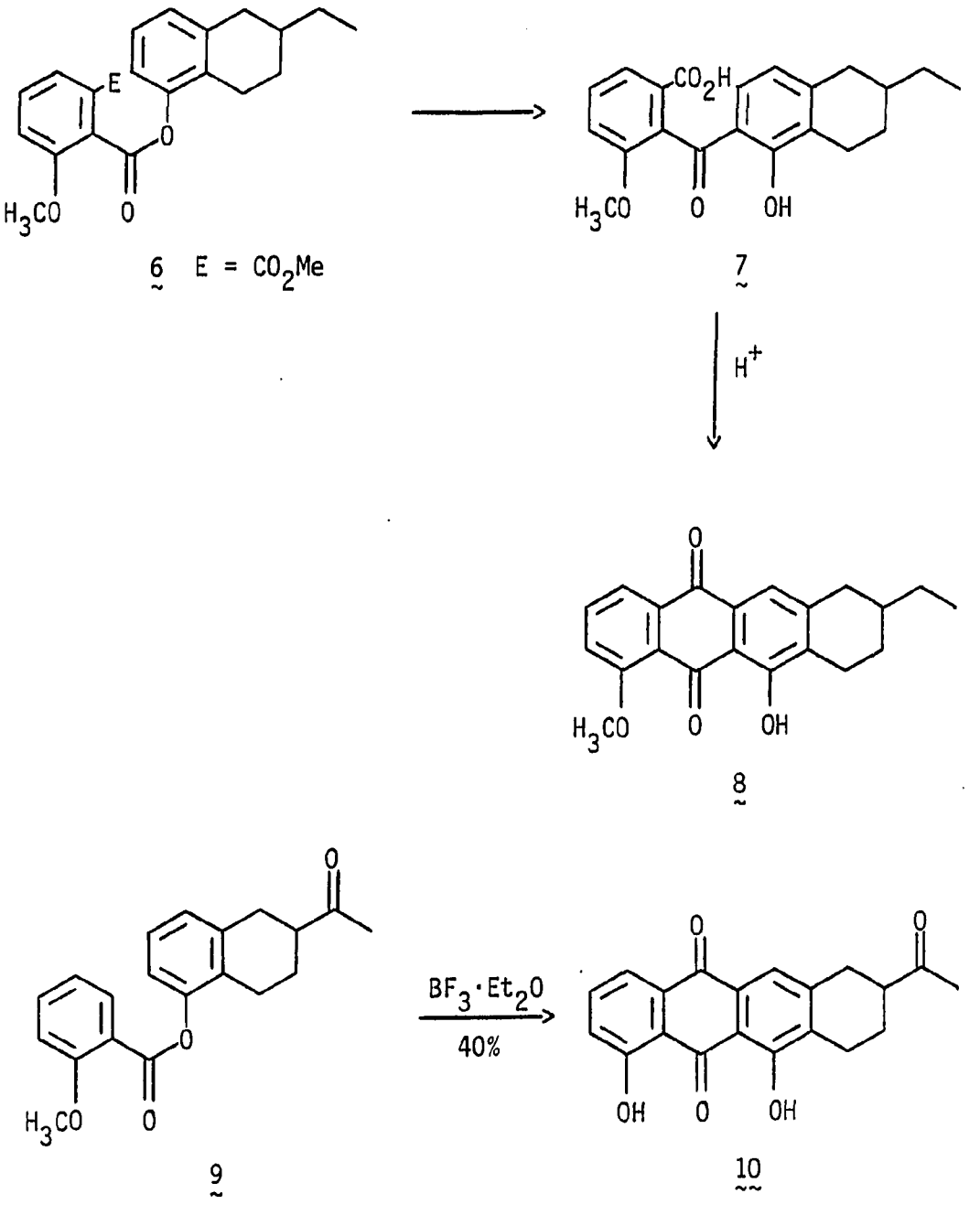
In planning a total synthesis of 11-deoxyanthracyclines, one must address two distinctive problems. These problems are the regioselective construction of the linear tetracyclic skeleton and the introduction of the C-7 hydroxyl group. The latter problem is usually accomplished via a benzylic bromination/solvolysis sequence. However, the efficiency of this sequence varies from excellent for the aklavinone to poor for the 6-deoxyanthracyclines and daunomycin series. For the formation of the tetracyclic framework of 11-deoxyanthracyclines, synthetic chemists have relied on one (or more) of three general reaction classes: Friedel-Crafts acylation and alkylation, Diels-Alder reactions, and anionic reactions.

Friedel-Crafts reactions

The Friedel-Crafts reaction has played an important role in the synthesis of anthracyclines. Kimball et al.[22a] and Kim et al.[22b] have used a convergent AB + D strategy in their synthesis of 11-deoxydaunomycinone. The key step in controlling regiochemistry utilized the $SnCl_4$-catalyzed Friedel-Crafts alkylation of tetralin $\underset{\sim}{2}$ by 3-bromo-4-methoxyphthalide $\underset{\sim}{1}$. Transformation of phthalide $\underset{\sim}{3}$ to anthraquinone $\underset{\sim}{4}$ was accomplished in good yield via hydrogenolysis, cyclization, and oxidation. Anthraquinone $\underset{\sim}{4}$ was then successfully converted to 11-deoxydaunomycinone via the intermediate $\underset{\sim}{5}$. Rama Rao and coworkers[23] have reported a similar synthesis.



Confalone and Pizzolato[24] have synthesized aklavinone by use of the Fries rearrangement. The o-hydroxybenzophenone 7, the product of an ortho-specific Lewis acid catalyzed Fries rearrangement, underwent Friedel-Crafts ring closure in the presence of acid to provide the anthraquinone 8 in 57% yield. The latter compound was then elaborated in a lengthy sequence into aklavinone. Although the Confalone synthesis is regiocontrolled, the overall yield is extremely poor. A similar approach was examined by Rama Rao and coworkers[25] who prepared an 11-deoxy compound 10 by BF_3-catalyzed Fries rearrangement of 9.



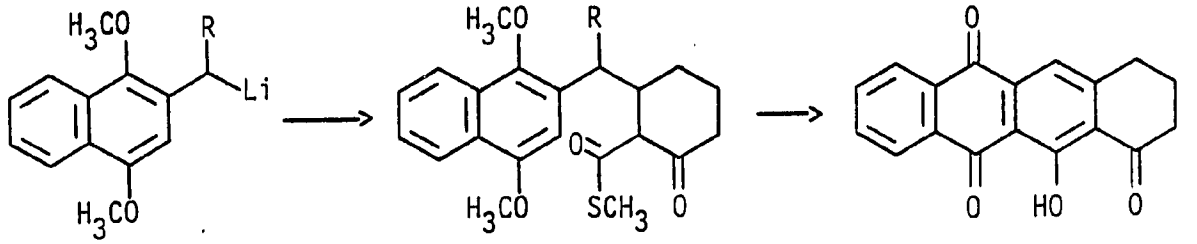
6 E = CO_2Me 7 8 9 10

Anionic reactions

The specific generation of anionic centers in one building block and acceptor centers in another enables selective bond formations and,

therefore, excellent control of regiochemistry. There are many possible first bond formations; however, Michael addition and aromatic directed ortho metallation are most often employed. Although the coupling of the two building blocks is usually a two step process (the second step is often a Friedel-Crafts reaction), many condensations can, in practice, be conducted in a single reaction vessel.

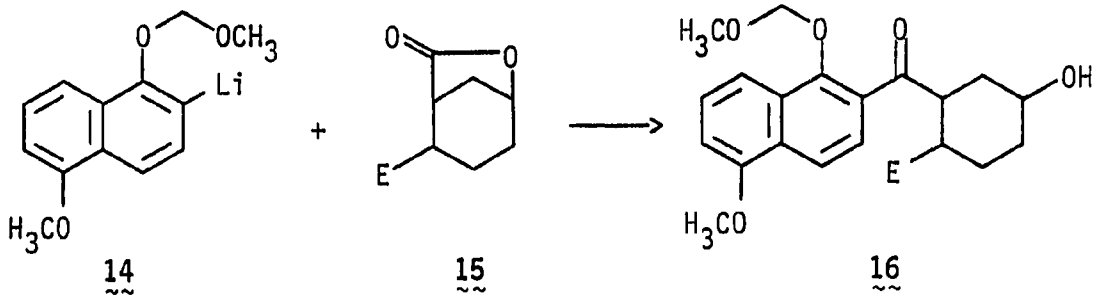
Vedejs and coworkers[26] have used an A + CD strategy in their synthesis of a 4-demethoxy-11-deoxyanthracycline intermediate which possesses the necessary oxygenation at C-7. A 1,4-addition of benzyl anion 11 to a cyclohexenone and subsequent trapping of the resulting enolate afforded thioester 12 in 66% yield. Cyclization of thioester 12 with cuprous triflate and oxidation with silver (II) oxide produced anthraquinone 13 in 56% yield. Thioester 12 is an ideal enolate carboxylation product because it can be cyclized without activation.



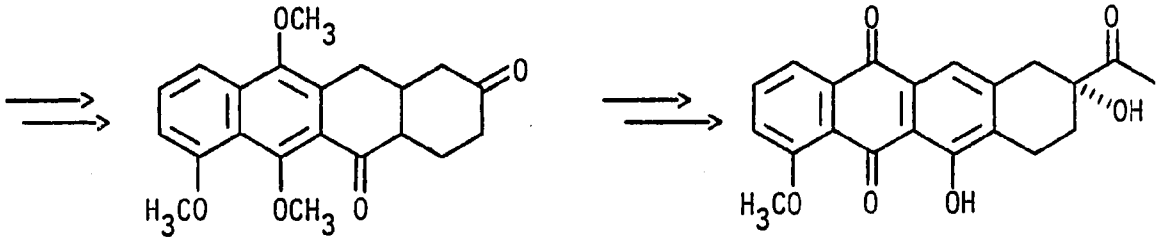
11 12 R = $Si(CH_3)_3$ 13

Another A + CD approach to 11-deoxydaunomycinone involved the addition of the metallated naphthalene 14 as the nucleophilic CD ring synthon to bicyclic lactone 15 to produce keto ester 16 in 73% yield. The keto ester was converted to tetracyclic diketone 17 in eight steps.

Anthraquinone 5 was obtained in 29% overall yield from tetracyclic diketone 17 in six additional steps.[27] The use of ortho-lithiated



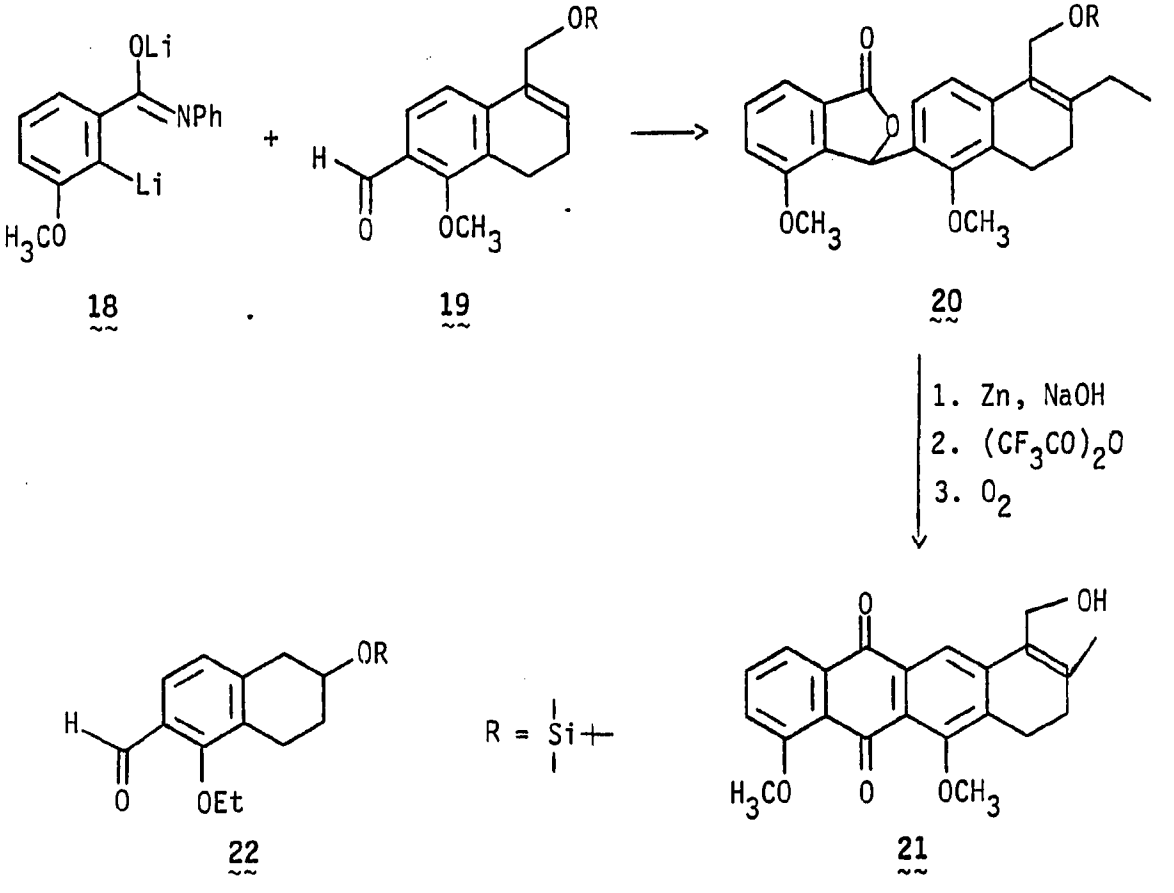
14 15 16



17 E = CO_2CH_3 5

benzamides for the regiospecific construction of anthraquinones was reported virtually simultaneously by several research groups.[28-30] This method was successfully applied by Kende and coworkers[31] for the syntheses of several 11-deoxyanthracyclinones. Condensation of a nucleophilic D-ring carboxamide 18 with a preformed bicyclic A/B-ring aldehyde 19 produced phthalide 20 in 80% yield. Hydrogenolysis of the phthalide and Friedel-Crafts ring closure afforded the anthraquinone 21 in good yield after aerial oxidation. One advantage of this route is that an enantioselective synthesis of aklavinone can be realized in 53% ee using the procedure of Sharpless for the asymmetric epoxidation of

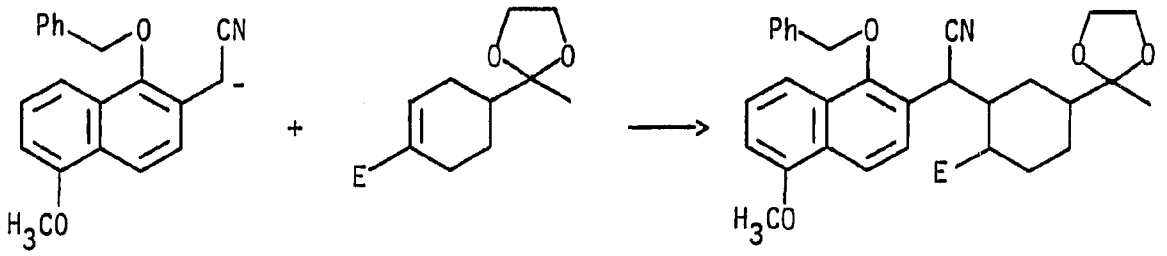
allylic alcohol 21. Furthermore, with the use of bicyclic aldehyde 22 as the A/B ring synthon, 11-deoxydaunomycin can also be prepared.[31a]



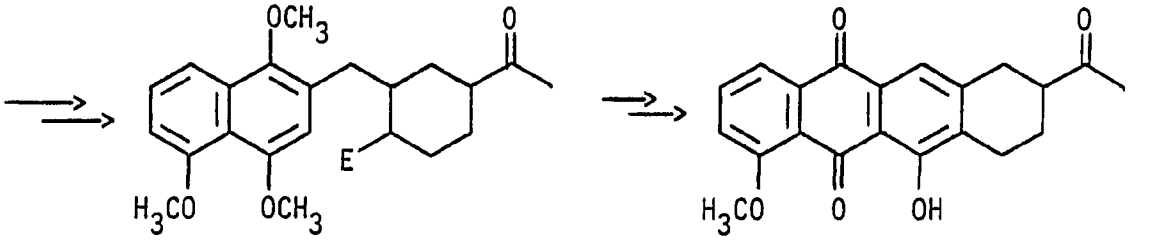
18 19 20

22 21

Parker and Tallman[32] made use of the Michael addition of the benzylic cyanide 23 to the cyclic α,β-unsaturated ester 24 for the regioselective synthesis of the precursor 25. The further transformation to the tetracyclic compound 27 is accomplished via a reductive elimination of the cyano group, Friedel-Crafts ring closure, and oxidation. Although Parker's synthesis is regioselective, this route suffers from a lengthy sequence and low overall yield.

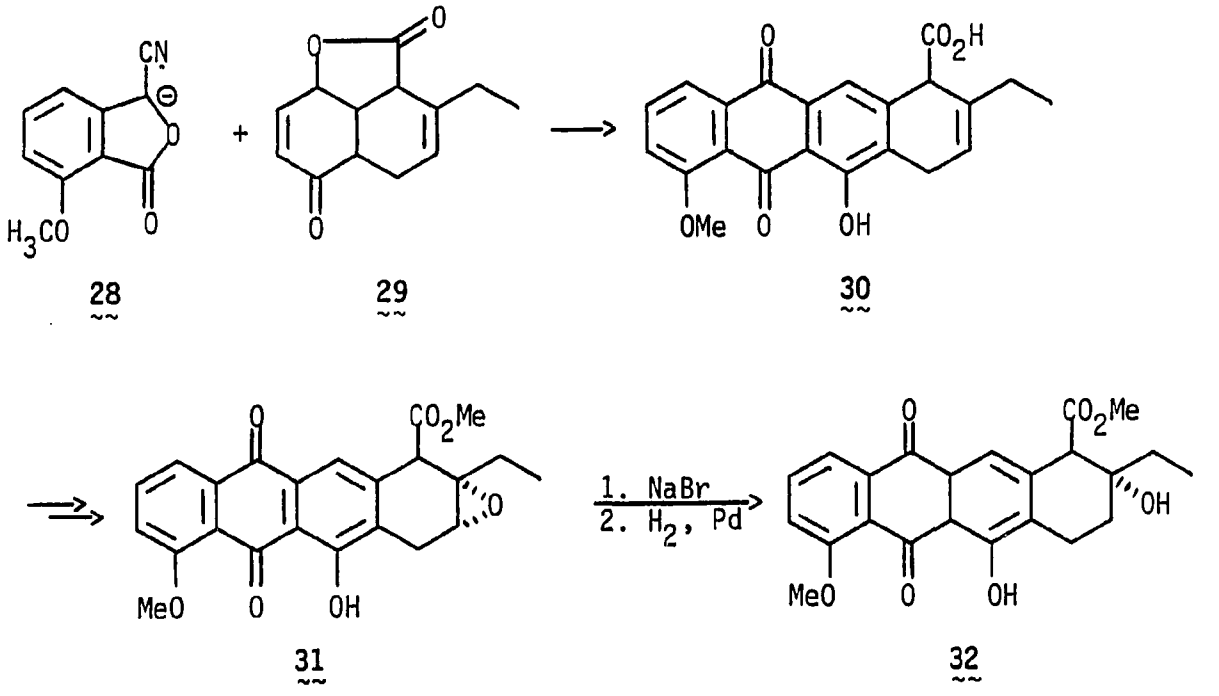


23 24 25



26 E = CO_2Me 27

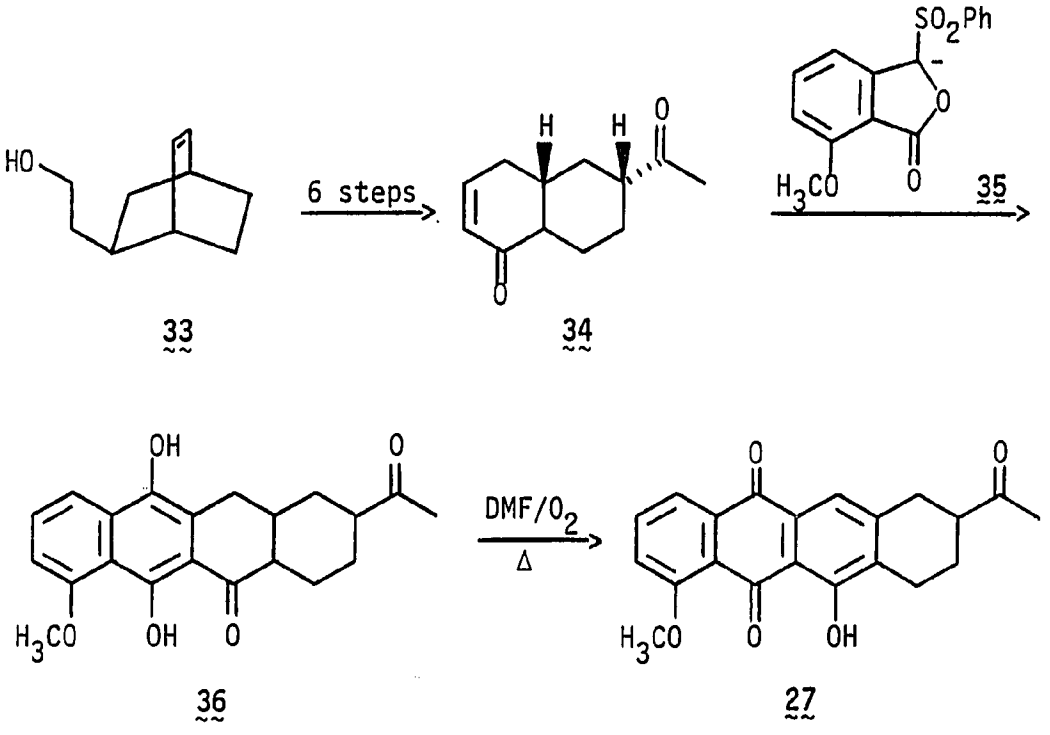
Kraus and coworkers[33] have developed a general synthetic methodology for annulating quinones utilizing the conjugate addition of cyanophthalide anions to unsaturated ketones. This method was neatly demonstrated by Li et al.[34] in the convergent synthesis of aklavinone. The coupling of phthalide anion 28 with the bicyclic enone 29 afforded anthraquinone 30 in good yield after aerial oxidation. Conversion of 30 to the aklavinone precursor 32 involved a stereoelectronically controlled epoxide ring opening of 31 with sodium bromide and hydrogenation of the resulting bromide.



28 29 30 31 32

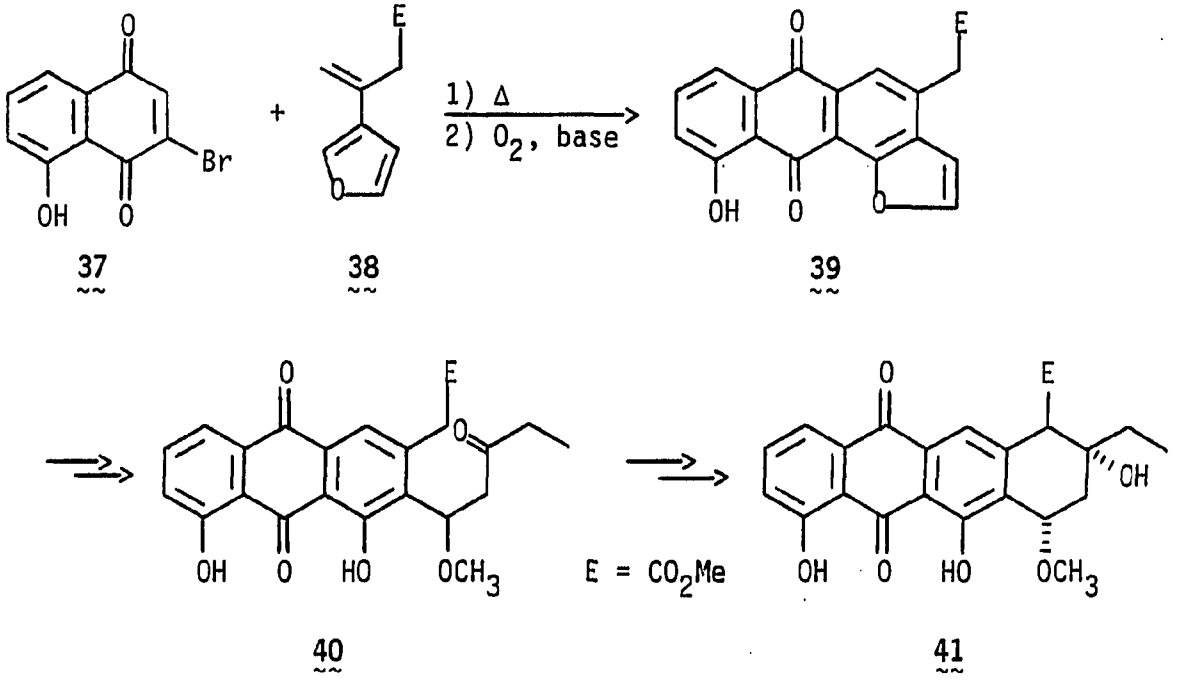
Hauser and coworkers,[35] on the other hand, made use of phthalide sulfones in their synthesis of 11-deoxydaunomycinone. Key features of their synthesis were the use of bicyclooctenol 33 as a precursor to the acetyl-substituted naphthalenone 34 which served as a synthon for rings A and B. Condensation of two equivalents of 34 with the anion of phthalide sulfone 35 furnished the tetracyclic product 36 regiospecifically, which was transformed to the anthraquinone 27 in a single step. An analogous approach to aklavinone was also reported by the same author.[35]

Intramolecular cyclization of an anthraquinone intermediate has been an important strategy in the syntheses of 11-deoxyanthracyclinones.[36] One of the first syntheses of aklavinone was based largely upon this strategy.[37] Anthraquinone 40 was prepared from benzofuran 39 in 70% yield via ozonolysis and aldol condensation.



33 34 36 27

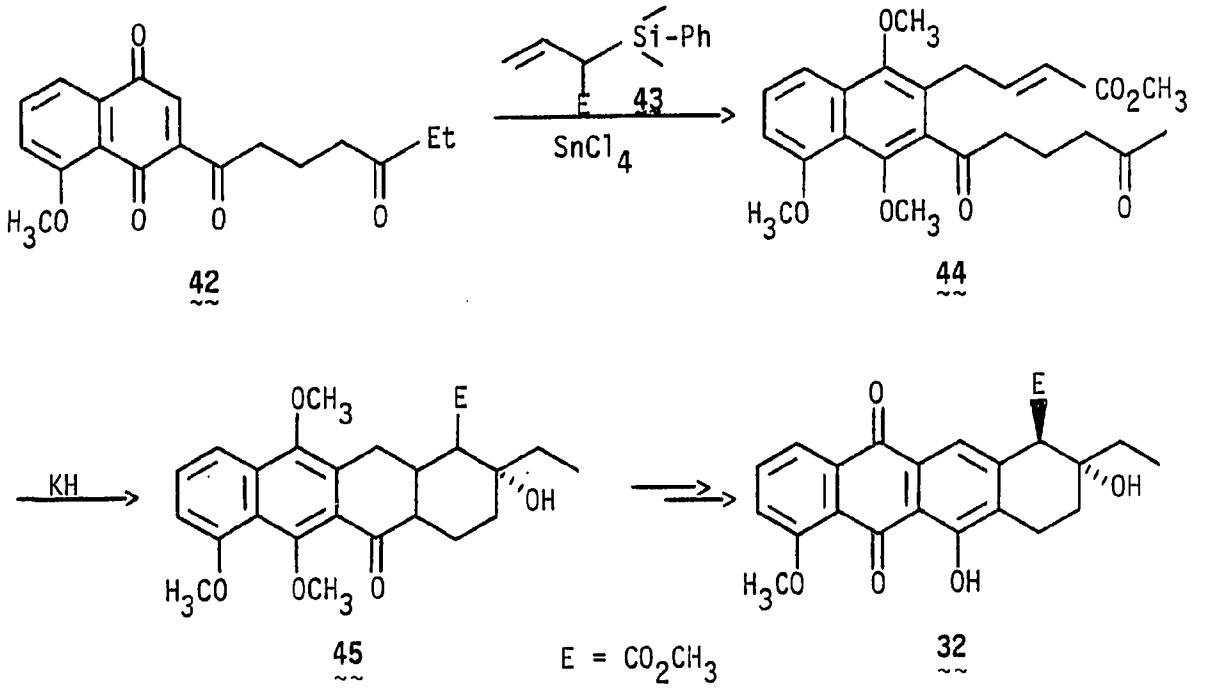
Treatment of ketoester 40 with potassium carbonate afforded a mixture of diastereomeric aldol products containing the correct isomer 41 as a minor product in 36% yield. Fortunately, all of the isomers could be equilibrated to the desired relative stereochemistry by a combination of acidic and basic treatment to afford 41 in approximately 60% yield. Although little stereocontrol was accomplished in the cyclization, this is the only synthesis of aklavinone in which functionality at C-7 is intact prior to the formation of the tetracyclic system. Furthermore, this route has been extended to the asymmetric syntheses of aklavinone and 11-deoxydaunomycinone.[37b] An analogous intramolecular condensation was later reported by Krohn.[38]



37 38 39 40 41

A similar approach was used by Maruyama and coworkers[39a] in their synthesis of aklavinone; however, both A and B rings were formed via a sequential Michael addition-aldol condensation ("zipper reaction"). The bicyclic compound 44 which resembles the tricyclic ketoesters was obtained by Michael addition of the silyl ether 43 to the naphthoquinone 42. Subsequent treatment of 44 with potassium hydride in the presence of a [2.2.2] cryptand provided 45 in 62% yield. In this biomimetic reaction, the presence of the crown ether was crucial to obtain a favorable mixture of diastereomers at C-9 and C-10.[39b] Oxidation to the quinone and aromatization of the B ring afforded 7-deoxyaklavinone 32.

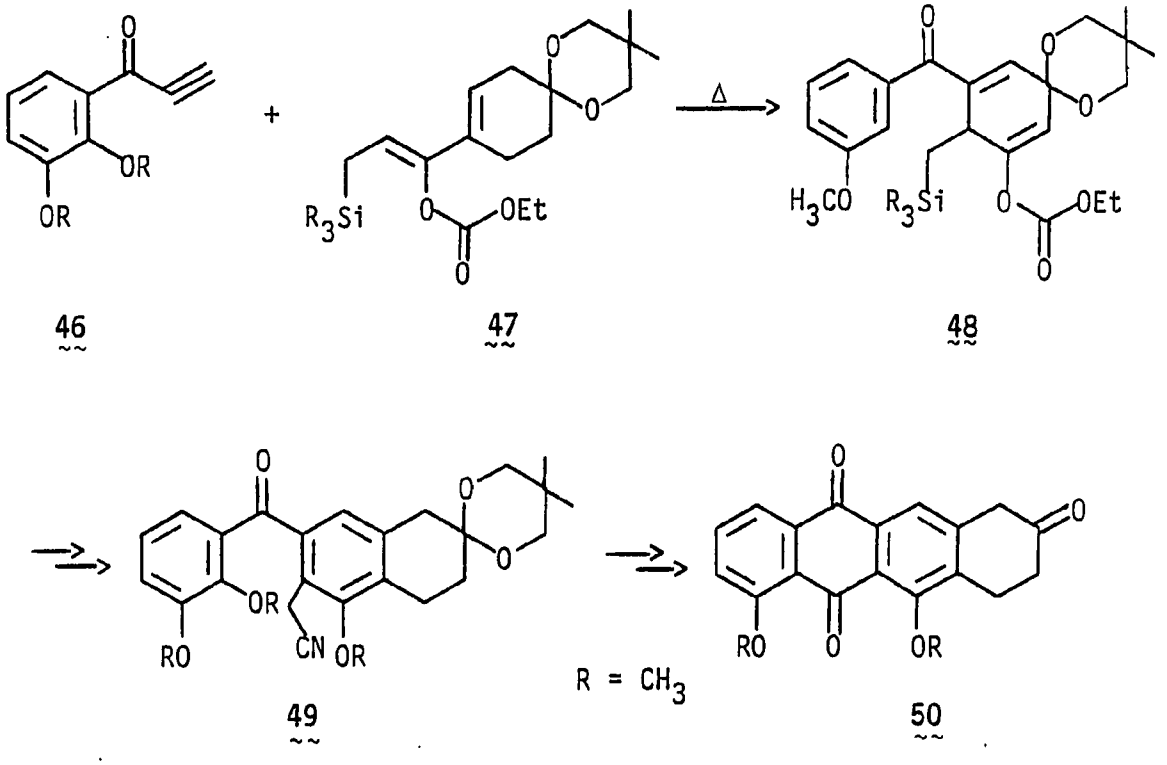
Vedejs and Nader[40] have reported a silicon mediated approach to the 11-deoxyanthracyclinones. Diels-Alder cycloaddition of ketoacethylene 46 and diene 47 gave adduct 48 in 86% yield and the isomeric adduct in 8%



42 44 45 32

yield. Adduct 48 was then transformed into the benzyl cyanide 49 in five steps. Hassall cyclization, oxidation, and deketalization produced anthraquinone 50 in a good overall yield.

As with the Friedel-Crafts acylation, the Marschalk reaction has been widely used as an initial step or as an end step in the formation of the tetracyclic system. The strategy employed by Krohn and Sarstedt[41] demonstrates the principle of this frequently used reaction. The reduction of the anthraquinone 51 with dithionite in aqueous alkali produced the hydroquinone 52, in which the electron density of the arene for an electrophilic attack by aldehyde was considerably increased as compared to that in the anthraquinone 51. Thus, the reactive species 52 was generated by a kind of redox umpolung from 51. During the

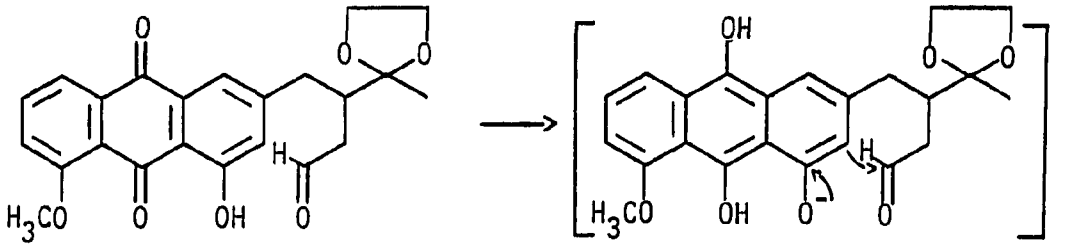


46 47 48

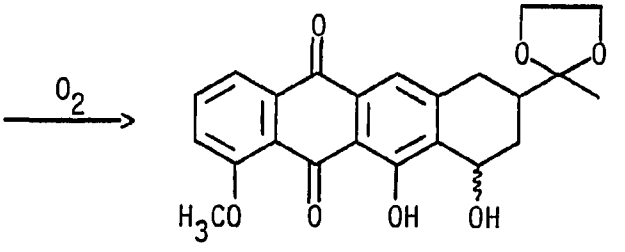
49 50

cyclization of the aldehyde 51, the benzylic hydroxy group could be preserved by decreasing the reaction temperature.

Nucleophilic additions to anthraquinones are a useful supplement to the Marschalk reaction insofar as the ortho-phenolic group is not a necessary prerequisite for the cyclization. This is demonstrated quite nicely in the synthetic approach to aklavinone by Cava et al.[42] A Michael addition of the anion of phenylthiomethyl cyanide 55 to the enone 54, followed by vicarious nucleophilic substitution onto the anthraquinone moiety provided the aklavinone precursor 56 after expulsion

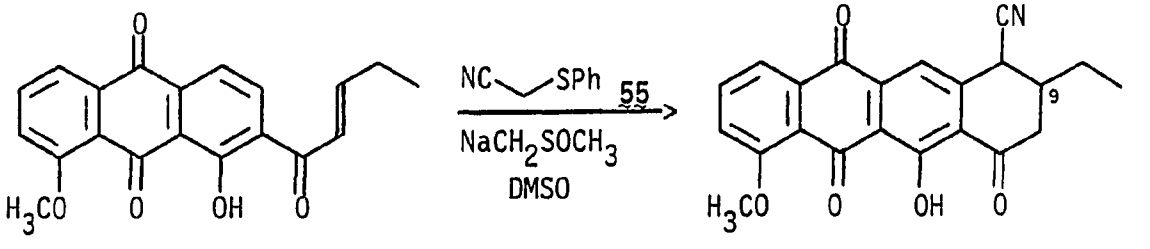


51 52



53

of thiophenoxide. Unfortunately, the methods of Cava do not allow a direct introduction of an hydroxy group at C-9.



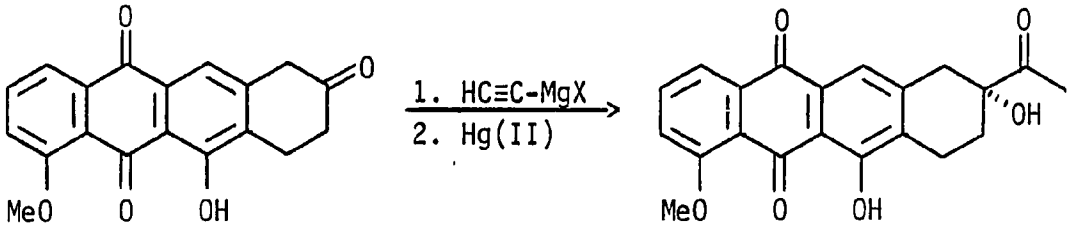
54 56

Diels-Alder reactions

The application of the Diels-Alder reaction to build up the tetracyclic ring system of 11-deoxyanthracyclines has been widely explored and represents one of the most direct and versatile approaches.

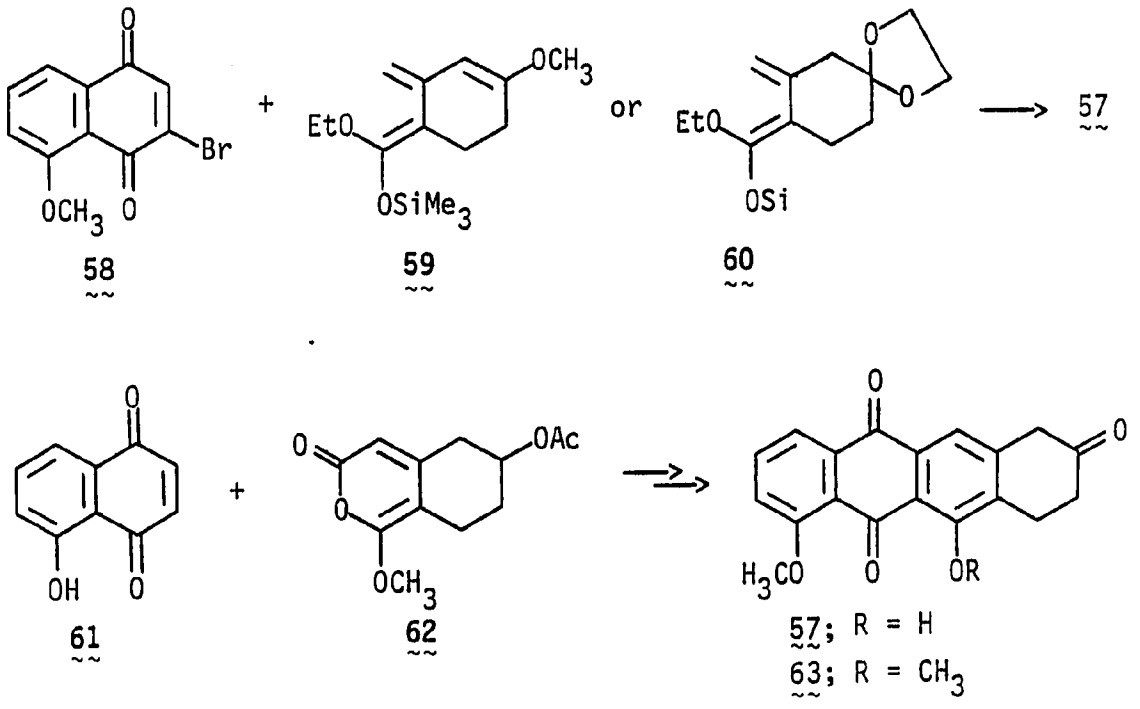
As in the case of the phthalide annulation methodology, the tetracyclic framework is amenable to a highly convergent A + CD strategy in which derivatives of juglone are extensively used as the CD-dienophile.

Early in 1980, it was believed that if efficient and regiospecific routes to the 11-deoxytetracyclic ketone 57 could be devised, the introduction of a C-9 side chain by known methods would lead to a practical synthesis of 11-deoxydaunomycinone.

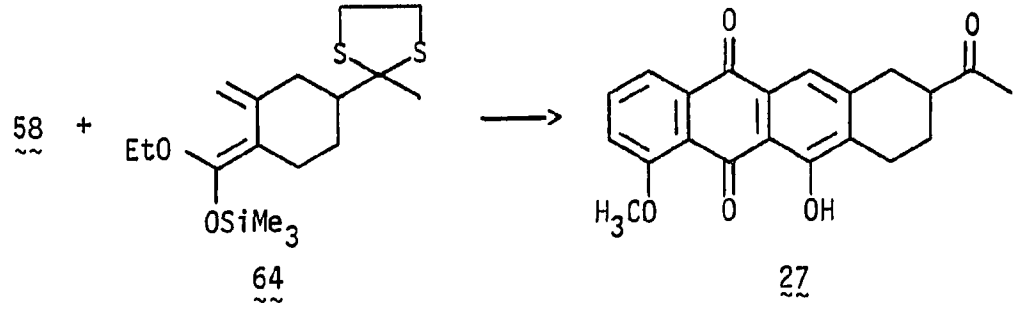


57 5

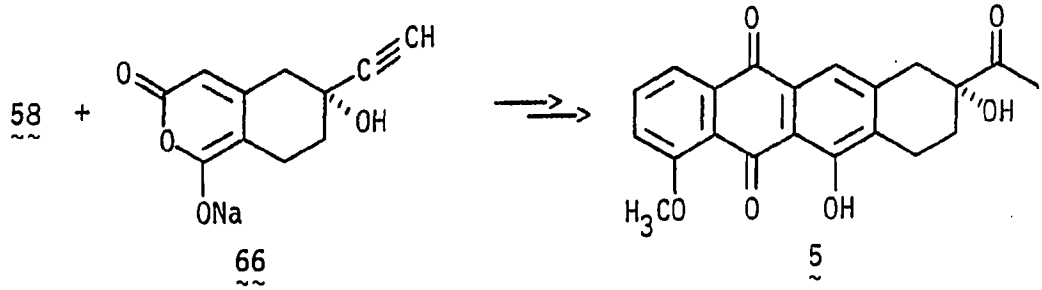
Based upon this premise, Gesson et al.[43] and Bauman et al.[44] independently developed a convergent and regioselective synthesis of ketone 57 by a Diels-Alder sequence involving addition of the ketene acetals 59 or 60 to the bromojuglone methyl ether 58. In these cases the bromine atom directs the regioselectivity and facilitates simultaneously the aromatization of the B ring with elimination of HBr and alcohol. Jung and coworkers[45] also prepared 63 by the cycloaddition of juglone 61 to the bicyclic 6-alkoxypyranone 62 followed by aromatization with carbon dioxide elimination.



Unfortunately, access to tetracyclic ketone 57 did not lead smoothly to the 11-deoxydaunomycinone. It was found later that the conventional ethynylation at C-9 with HC≡C-MgBr proceeded in very poor yield (22%) due to enolization. To circumvent this problem, an alternative approach using the AB building block with a side chain 64 has been devised by Gesson and Mondon.[46] Cycloaddition of vinyl ketene acetal 64 with 58 and subsequent dethioketalization produced anthraquinone 27 in good yield. However, conversion of anthraquinone 27 to 11-deoxydaunomycinone was accomplished in a poor overall yield. A related approach to 11-deoxydaunomycinone reported by Tamura and coworkers[47] utilized the strong base induced cycloaddition of homophthalic anhydride 66 to the bromojuglone methyl ether 58.

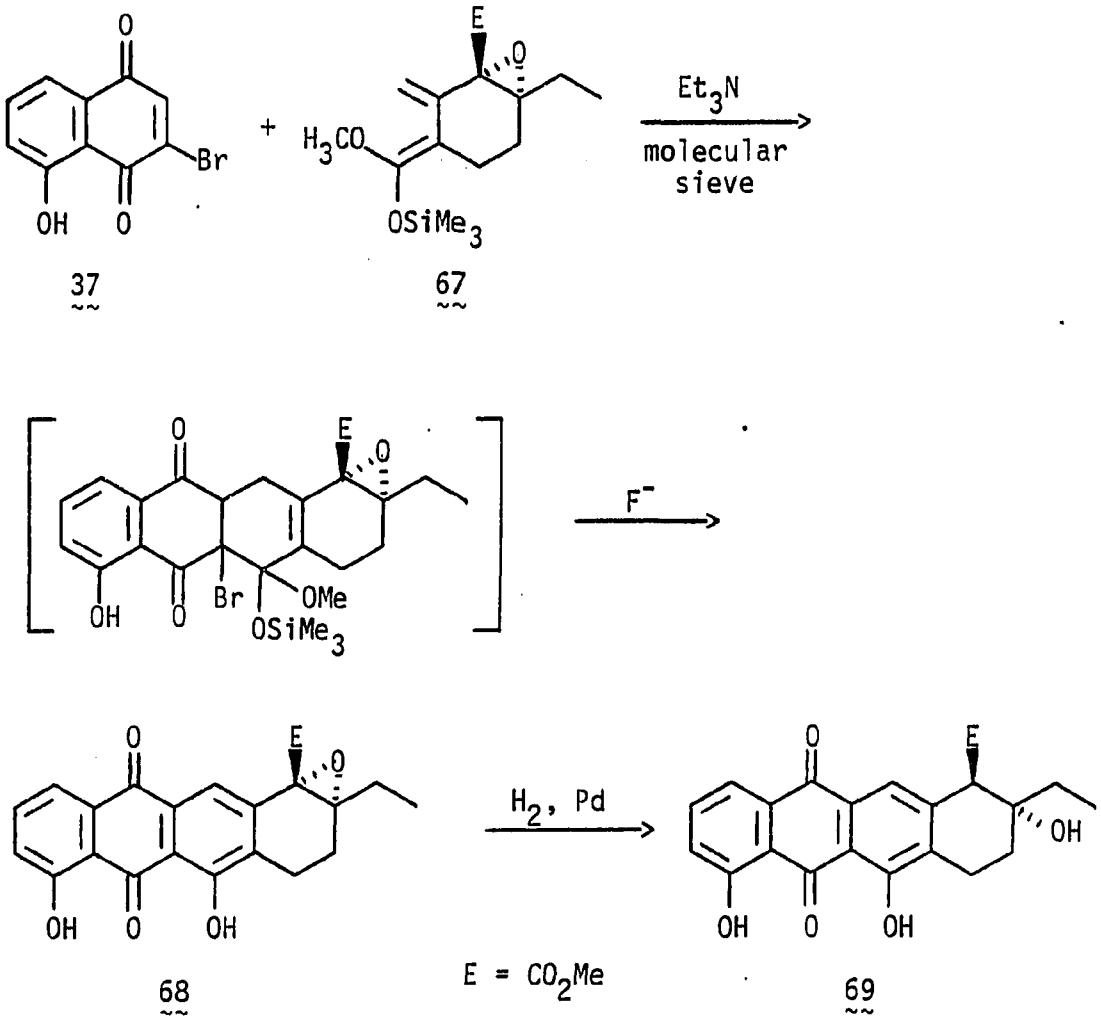


64 27



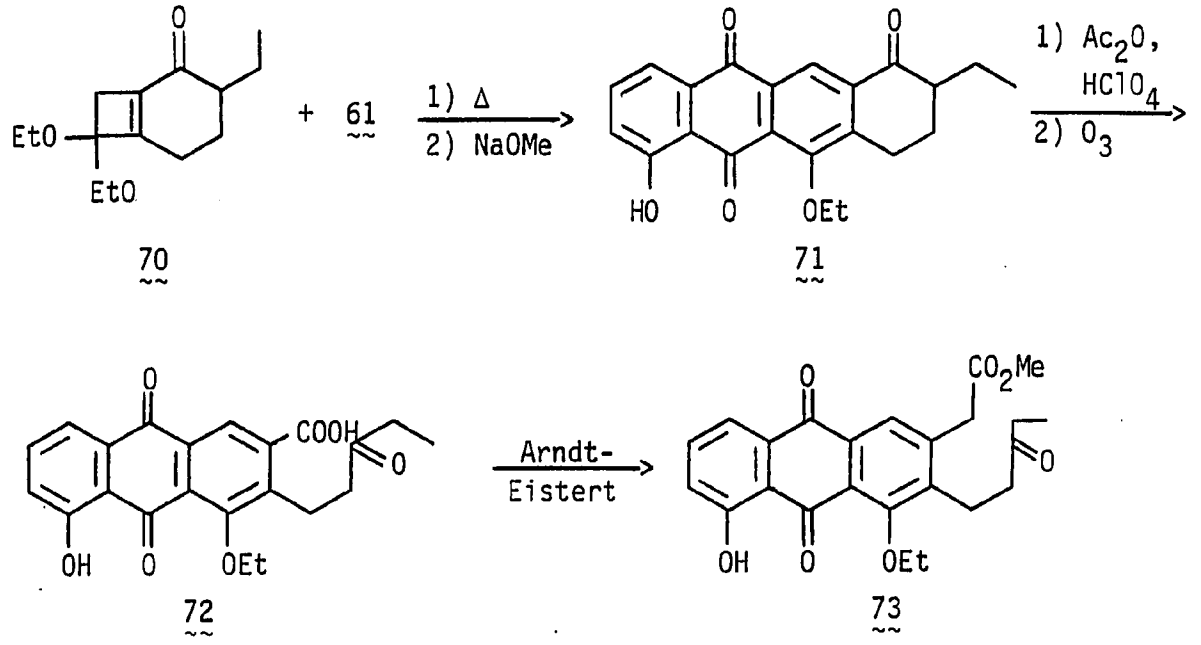
66 5

Bauman and coworkers[48] were able to realize the use of the highly functionalized exocyclic ketene acetal 67 in a convergent synthesis of aklavinone via the intermediate 68. Carefully controlled reaction conditions were necessary in the Diels-Alder reaction to prevent aromatization of the primary adduct. Anthraquinone 68 could be readily transformed to aklavinone using the previously defined procedure of Confalone and Pizzolato[24] and Kende et al.[31] With the use of different naphthoquinones as dienophiles, aklavinone derivatives with a variety of substituents in ring D could also be prepared.



Boeckmann and Sum,[49] on the other hand, generated a vinyl ketene acetal *in situ* by the thermolysis of cyclobutene derivatives for the synthesis of the deoxyanthracyclines. Thus, heating cyclobutene 70 in the presence of juglone 61 produced a 4.4:1 mixture of anthraquinone 71 and its regioisomer. Unfortunately, direct conversion of the major isomer 71 to aklavinone proved troublesome. Ultimately, Arndt-Eistert

homologation of an A-ring cleavage product 72 afforded 73 which was transformed to aklavinone by an intramolecular aldol condensation.



In summary, the anthracyclines are an important class of antitumor antibiotics which have proven successful in clinical trials. However, their cardiotoxicity has been a major drawback of these drugs. Thus, a search for new anthracyclines with better therapeutic indices has been of great interest. The recent discovery of new anthracyclines such as 11-deoxydaunomycin and aclacinomyin A, which show reduced cardiotoxicity, has stimulated the development of an efficient route toward such 11-deoxy aglycones. The synthetic approaches to these compounds are varied and include Friedel-Crafts acylation and alkylation, Diels-Alder

cycloaddition, and anionic approaches; overall, these strategies have been used effectively to construct the tetracylic system, but improvements to these strategies are needed.

RESULTS AND DISCUSSION

After more than a decade of intense interest, the synthesis of anthracycline antibiotics still remains an active area of research.[19,20] In large part, this is due to the isolation and characterization of new and highly active anthracyclines. Among these, 11-deoxydaunomycin, aclacinomycin, and nogalomycin are perhaps the most active of newer anthracyclines. One structural feature which these compounds have in common is that the hydroxyl group which is present at C-11 in most anthracyclines has been replaced by a hydrogen atom. These 11-deoxyanthracyclines exhibit dramatically lower cardiac toxicities than their 11-hydroxy counterparts. As a consequence, aclacinomycin has become a clinically useful drug.[6,7]

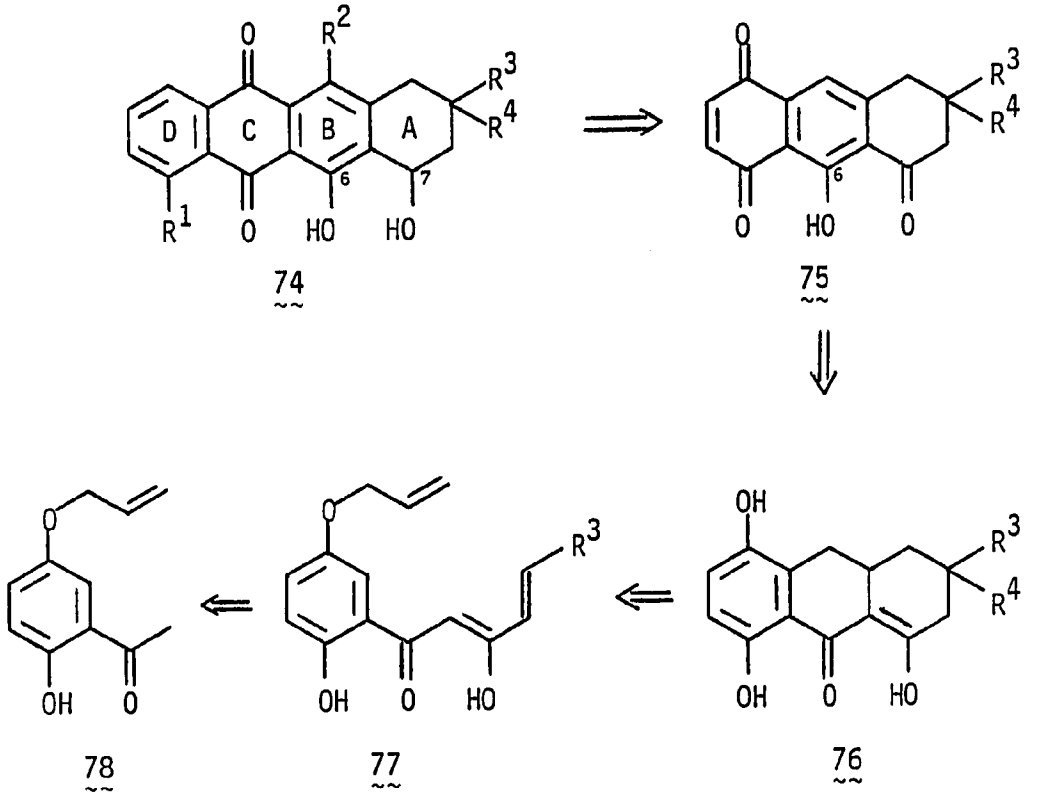
General Strategy

While many elegant solutions to the synthesis of 11-deoxyanthracyclinones, the aglycones of anthracycline antibiotics, have been advanced, some problems still remain. For example, a majority of the routes involve the preparation of a 7,11-dideoxy compound with anticipation that the required C-7 hydroxyl group could be introduced in the last step via a benzylic bromination/solvolysis reaction sequence. This method, however, is inadequate especially with regard to scale-up at preparative levels.[50] Furthermore, the optimal solvolysis conditions (dilute NaOH, $NaHCO_3$, H_2O, etc.) have to be found for every single compound. We feel that a better strategy would be to incorporate a hydroxyl group or its precursor into a synthetic intermediate at a much

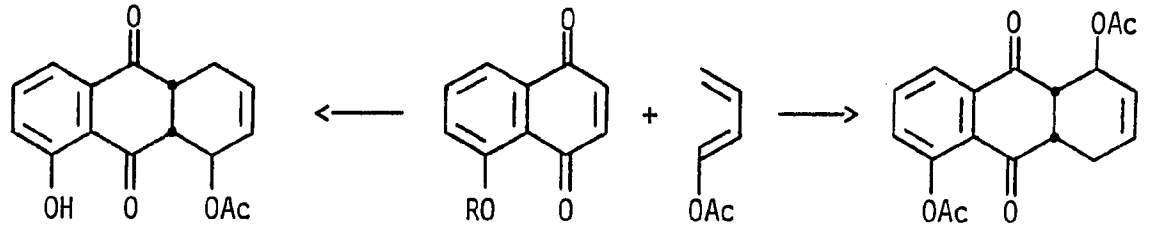
earlier stage. Additionally, the recent interest[51] in anthracyclines that are halogenated in the D ring has increased the demand for a direct synthetic route that allows rapid entry to a variety of D ring-modified compounds.

Previous work from our laboratories had demonstrated the utility of a tandem Claisen-Diels-Alder reaction for the rapid construction of a linearly fused polycyclic system suitable for anthracycline and tetracycline skeletons.[52] It was hoped to use this reaction as a key step for our approach to 11-deoxyanthracyclines. The general strategy we selected for our present work is outlined in Scheme 1.

Scheme 1



We envisioned the tricyclic quinone 75 as a versatile CBA ring system for the synthesis of 11-deoxyanthracyclinones, especially those with a modified D ring. It contains the requisite B and C ring and latent functionality for the A ring. Quinone 75 in turn could be prepared in only three steps starting from 2-hydroxy-5-allyloxy-acetophenone 73. The tandem Claisen-Diels-Alder reactions (77 → 76) followed by oxidative aromatization (76 → 75) would afford 75. Subsequent Diels-Alder reaction of 75 with a suitable diene would then assemble the tetracyclic framework of the anthracyclinone nucleus with high regiochemical control. It was anticipated that the peri-hydroxyl group at C-6 (anthracycline numbering) would direct the regiochemistry of this cycloaddition, based on ample literature precedents.[53-57] Specifically, in connection with studies directed toward the synthesis of terramycin, Inhoffen and Muxfeldt[53] observed that while the Diels-Alder reaction of 5-hydroxy-1,4-naphthoquinone 61 with 1-acetoxy-1,3-butadiene gives a product wherein 80 is the principal regioisomer, use of juglone acetate 79 leads to a reversal in regiochemistry, affording 81 as the principal adduct. This general trend



80

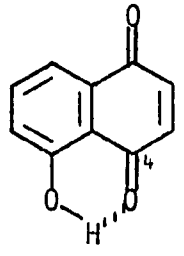
61 R = H

79 R = OAc

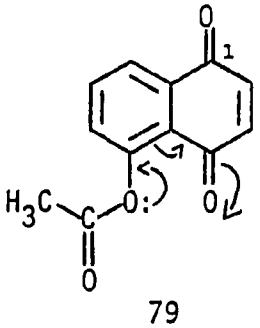
81

has also been observed for a variety of diene systems by several groups.[54-57]

The rationale for this effect, alluded to initially by Inhoffen and further developed by Birch and Powell[54] and Kelly et al.,[55] revolves around the strong hydrogen bonding present in quinone 61. This serves as an "internal Lewis acid", polarizing the unsaturated system and resulting in the C-4 carbonyl serving as the dominant director of cycloaddition. Alternatively, delocalization of the lone pair electrons on the oxygen of the acetate into the C-4 carbonyl is considered to dominate in the acetate 79, leading to reversal of the regiochemical result. This directing effect has often been used in anthracycline synthesis.



61



79

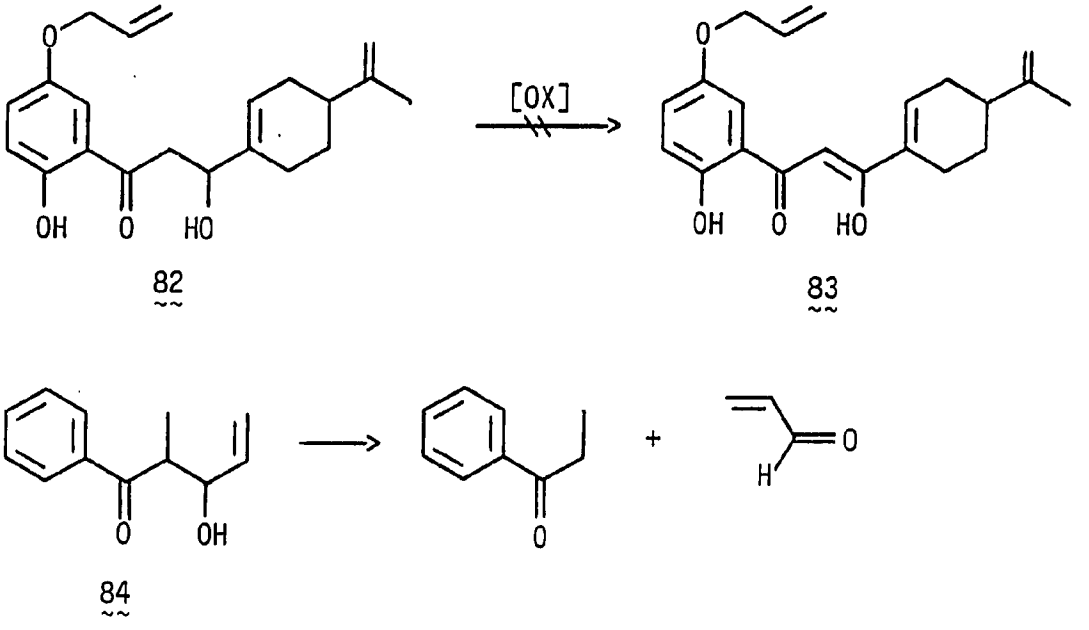
Based upon our earlier studies, we reasoned that the identification of a suitable group for R^3 (Scheme 1) was crucial to our approach to 11-deoxyanthracyclinones. This group must be compatible with the reaction conditions for both the acyl transfer reaction and the tandem Claisen-Diels-Alder reaction.

To explore the feasibility of our strategy outlined in Scheme 1, we required the β-diketones 77 as the CBA-ring precursors. However, the

absence of a reasonable route for preparing β-diketones such as 77 necessitated the development of an efficient method for their preparation. In the following section our efforts toward this end will be detailed. This will be followed by discussion of the tandem Claisen-Diels-Alder reaction.

Synthesis of β-diketones via a modified Baker-Venkataraman reaction

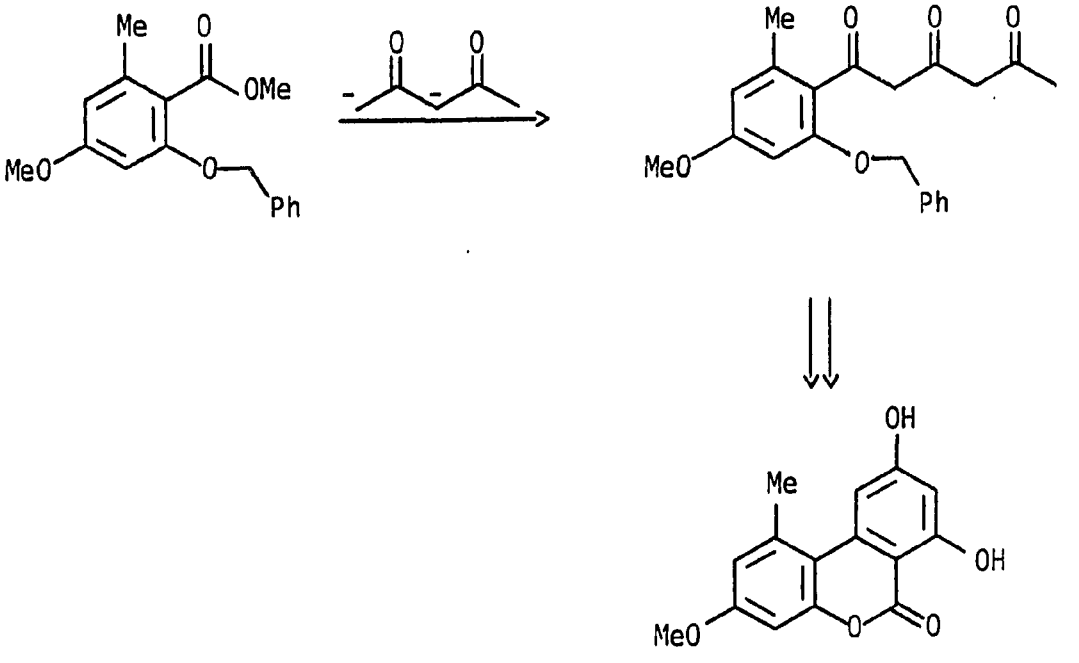
Early attempts in our laboratories to prepare β-diketone 83 from the corresponding β-hydroxy ketone 82 by way of oxidation were unsuccessful. Under oxidation conditions, the β-hydroxy ketone 82 either suffered fragmentation via a retro-aldol process or underwent β-elimination of water. Smith and Levenberg[58] have noted similar difficulties with oxidation of β-hydroxy compounds to β-diketones. They noted that oxidation of 84 produced only the retro-aldol products.



82 83

84

It is possible to avoid the oxidation step by using low temperature acylation of enolates with electrophiles such as esters, acid chlorides or acyl imidazoles. This will produce the β-diketone directly. Both Claisen reactions[59] and acetoacetic ester condensations[60] have been extensively used to produce β-diketones and β-ketoesters, respectively. Recently, Sandifer and coworkers have elegantly demonstrated the effectiveness of the Claisen reaction through several syntheses of polyketide-derived natural products.[61]

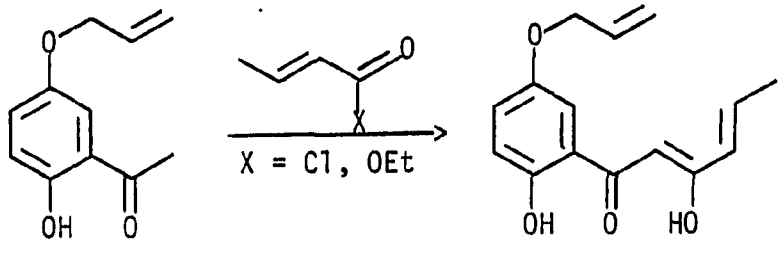


Both reactions, however, have some limitations. For example, significant problems are often encountered when esters bearing acidic hydrogen atoms are employed in the Claisen reaction. Additionally, yields tend to be poor unless the reaction conditions are rigorously defined.

Since the Claisen and acetoacetic ester condensations are often performed in an alcohol solvent, esters were the only acylation agents possible. When methods for the kinetic generation of enolate anions in aprotic media were developed,[62],[63] the acylation of enolates with anhydrides or acid chlorides provided a useful route to β-dicarbonyl compounds.[64] The major side reaction, o-acylation, could be minimized by inverse addition of the acid chloride.[65]

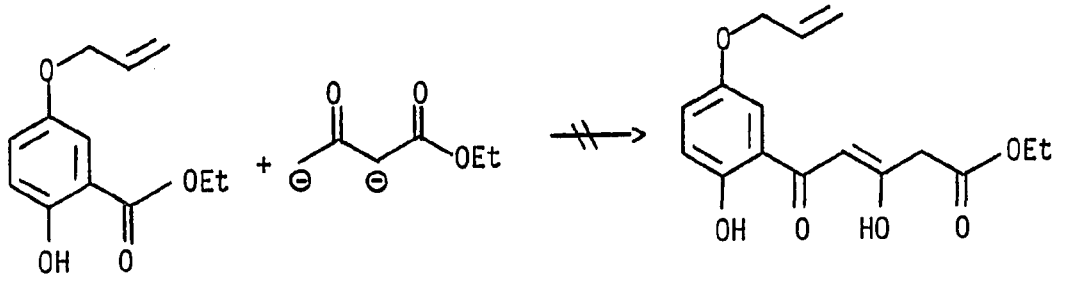
In order to prepare 86 by the above methods, acylation of o-hydroxy ketone 85 with crotonoyl chloride was examined. The reaction of the dianion of 85 (2.1 eq. LDA, 0° or -78°) with crotonoyl chloride under inverse conditions furnished a low yield (28%) of the desired β-diketone 86 due in large part to poor conversion. The low conversion can be best explained by considering that the product β-diketone 86 is acidic and quenches the unreacted enolate at a faster rate than acylation occurs.

Similar treatment of 85 with ethyl crotonate failed to give any detectable amount of 86 even when condensation was allowed to proceed for 24 hr. Use of KH, LDA, lithium 2,2,6,6-tetramethylpiperidide (LITMP), or potassium t-butoxide/t-butanol complex as base at varying temperatures

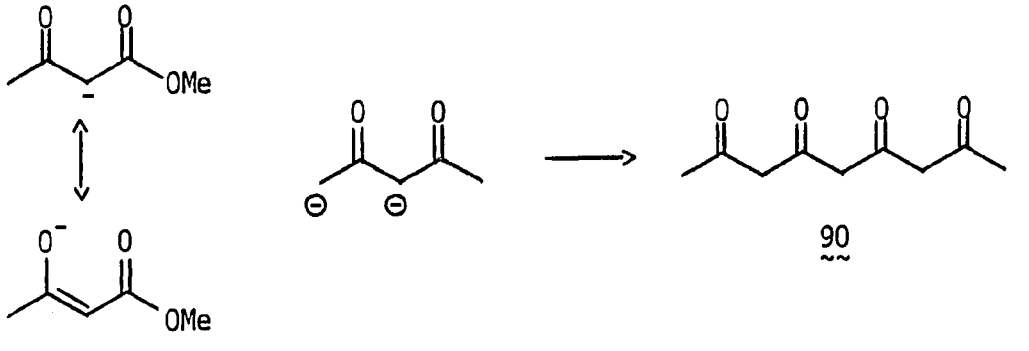


85 86

(-78° → 25°) yielded only recovered starting material. Attention was then turned to acylation of the dianion of ethyl acetoacetate with the lithium salt of benzoate ester 87. Precedents are available which suggest the feasibility of such anion-anion condensations.[66] For example, the monoanion of methyl acetoacetate 89 reacts with the dianion of 2,4-pentadione to form tetraketone 90. However, in our hands, ester 87 was recovered in high yield from the reaction mixture.



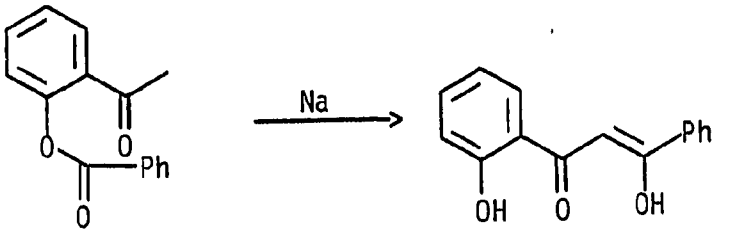
87 88



89 90

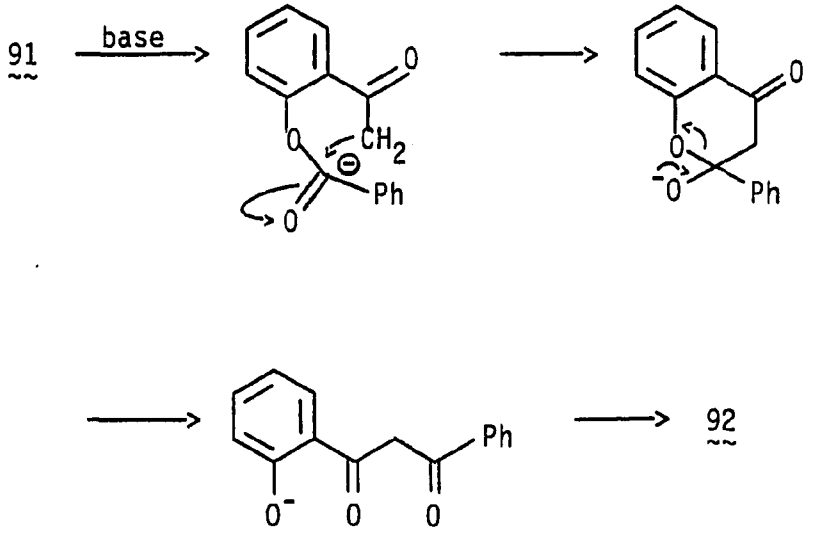
A literature search revealed that for certain systems, intramolecular acylation is possible. In the example shown below,[59] the Baker-Venkataraman reaction is used to generate an o-hydroxy β-diketone 92 from

o-benzoyloxyacetophenone 91 via an intramolecular Claisen condensation. This intramolecular acyl transfer reaction has become a major reaction in flavone chemistry.[67]



91 92

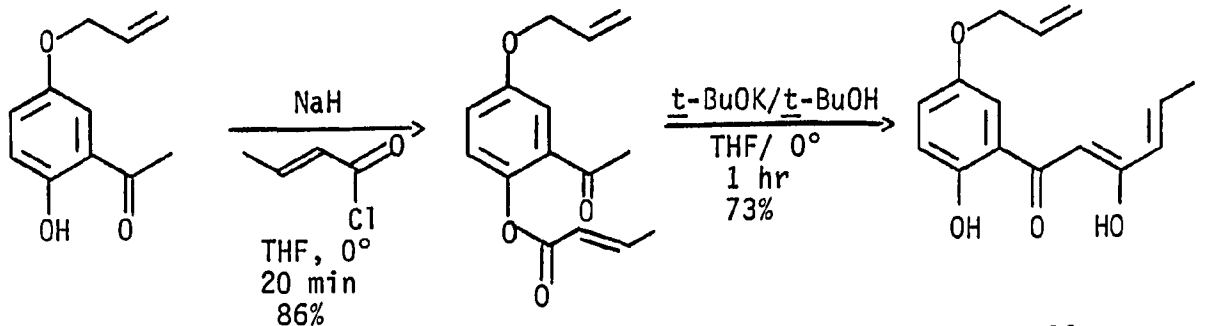
The detailed mechanism of this reaction involves the abstraction of the hydrogen α to the ketone carbonyl group followed by addition of the resulting anion to the carbonyl group of the ester, accompanied by displacement of the phenolate anion.



Interestingly, the use of the Baker-Venkataraman reaction appears to have been confined to the transfer of aromatic or heteroaromatic acyl

groups.[68] Additionally, the vigorous reaction conditions often employed would not be compatible with sensitive functionality. In order to prepare β-diketones such as 86, we decided to investigate the reaction to see if it could be extended to the transfer of aliphatic acyl groups.

Towards this end, the keto ester 93 was prepared by generation of the sodium phenoxide with sodium hydride followed by addition of crotonoyl chloride at 0°C in THF. The intramolecular acyl transfer was then examined using various reaction conditions (t-BuOK/t-BuOH, LDA; THF, CH_3CN, DMF; -75°, -25°). We found that the best results (73%) could be obtained when the reaction was carried out at 0°C in THF using two equivalents of potassium t-butoxide/t-butanol complex as a base. Other variations in the reaction conditions, using LDA as a base or using CH_3CN as a solvent, did afford the product 86 but in much lower yield. The



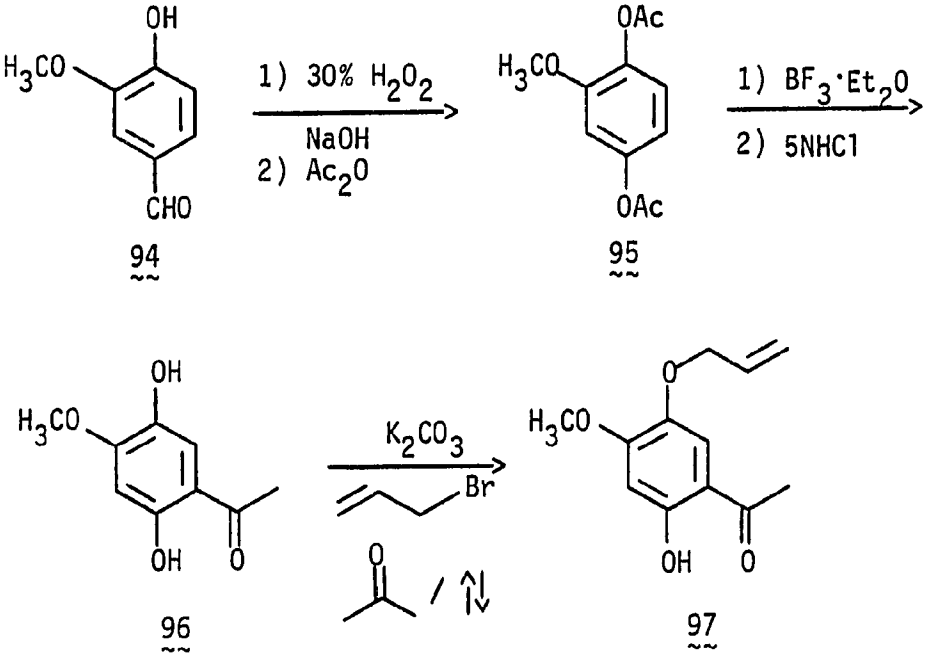
85 93 86

β-diketone 86 obtained exists completely in its enol form, as evidenced from the proton NMR spectrum showing two sharp singlets around 6.1 ppm and 14.7 ppm, corresponding to vinylic and enolic hydroxyl proton, respectively.

While the two step process was performed initially with the isolation of the keto ester 93, both reactions could, in principle, be conducted in the same reaction vessel with comparable yield. This proved to be the case. The optimized yield of 86 for the one-pot procedure was 71%.

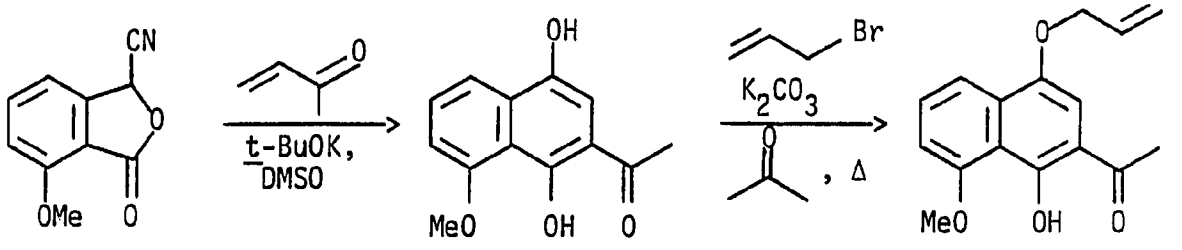
In order to explore the generality and utility of this reaction, various acid chlorides, as well as o-hydroxy ketones 97 and 100, were prepared and subjected to the reaction conditions described above. The acid chlorides used for this study were easily prepared from the readily available corresponding carboxylic acids by standard procedures employing thionyl chloride or oxalyl chloride.

The o-hydroxy ketone 97 was synthesized by a regiospecific BF_3-Et_2O catalyzed Fries rearrangement of the known diacetate[69] 95 followed by *in situ* hydrolysis of the resultant monoacetate with 5NHCl. The reaction of 96 with allyl bromide and potassium carbonate in refluxing acetone then afforded 97 in 73% yield.



94 95 96 97

The bicyclic o-hydroxy ketone 100 was prepared to see if the expected β-diketone product would undergo a tandem Claisen-Diels-Alder reaction to afford directly a tetracyclic compound. Treatment of cyanophthalide 98 with methyl vinyl ketone and potassium t-butoxide in dimethyl sulfoxide yielded hydroquinone 99 in 65~70% yield. Subsequent selective O-alkylation of 99 produced 100 in 68% yield.

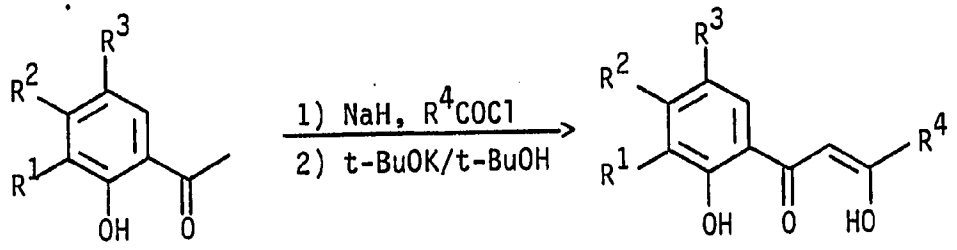


98 99 100

The result of a study of the acyl transfer reaction of o-hydroxy ketones 85, 97, 100, and 101 with a variety of acid chlorides are summarized in Table 1. A portion of the work has been recently published.[70]

The reaction was general and afforded good yields of several β-diketones. Noteworthy limitations are, however, apparent. When the ester group has α-protons that are comparable in acidity to the ketone (Entry 15), a mixture of products were obtained. In this case, the major products were derived from the ester enolate. Additionally, unsaturated acid chlorides 118-122, bearing electron withdrawing groups or electron donating groups in the β-position, failed to afford the desired β-diketones and resulted in the recovery of starting o-hydroxy ketone 85 (Entries 17~21).

Table 1. Synthesis of β-diketones

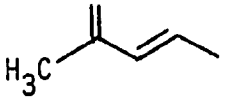
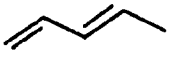
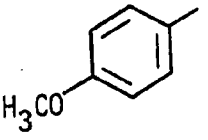


85: $R^1 = R^2 = H$, $R^3 = (CH_2=CH-CH_2-O-)$

97: $R^1 = H$, $R^2 = OCH_3$, $R^3 = (CH_2=CH-CH_2-O-)$

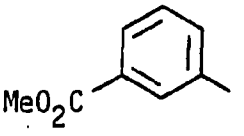
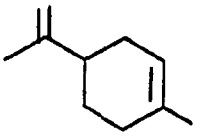
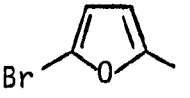
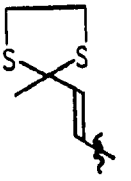
100: $R^1 = R^2 = -(C=CH-CH=C-)OCH_3$, $R^3 = (CH_2=CH-CH_2-O-)$

101: $R^1 = R^2 = R^3 = H$

Entry	o-Hydroxy Ketone	Acid chloride (R^4-COCl)	% Yield	β-Diketone
1	85	$H_3CCH=CH-$	71(30)[a]	86
2	85	$H_3C(CH=CH)_2$	72	102
3	85		62	103
4	85		70	104
5	85		69	105

[a]LDA added in second step instead of t-BuOk-t-BuOH.

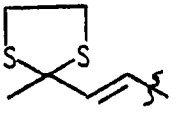
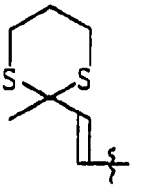
Table 1. Continued

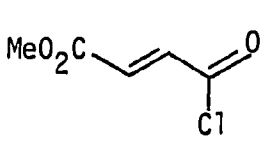
Entry	o-Hydroxy Ketone	Acid chloride (R^4-COCl)	% Yield	β-Diketone
6	85		68	106
7	85		64	83
8	85		50	107
9	97	$H_3C(CH{=}CH)_2$	68	108
10	100		64	109
11	101	$H_3CCH{=}CH-$	54	110
12	101	$PhCH{=}CH-$	61	111
13	101	$C_5H_{11}-$	52	112
14	101	$H_2C{=}CH-$	-[b]	
15	101	CH_3-	28	113
16	101	Ph-	64[c]	114

[b] TLC analysis indicated that the aryl ester had been formed. However, no recognizable products were obtained after addition of the t-BuOK-t-BuOH.

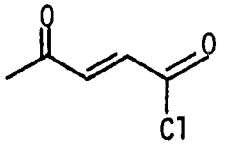
[c] Identical with known compound.[71]

Table 1. Continued

Entry	o-Hydroxy Ketone	Acid chloride (R^4-COCl)	% Yield	β-Diketone
17	85	$CH_3O_2CCH=CH-$	-[b]	-
18	85	$H_3CCOCH=CH-$	-[b]	-
19	85	$ClCH=CH-$	-[b]	-
20	85	$ClC(CH_3)=CH-$	-[b]	-
21	85	$H_3CO(CH_3)CH=CH-$	-[b]	-
22	97	$PhSCH=CH-$	64	115
23	85		76	116
24	85		72	117



118



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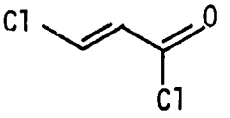
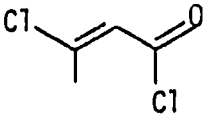
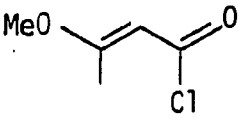


120



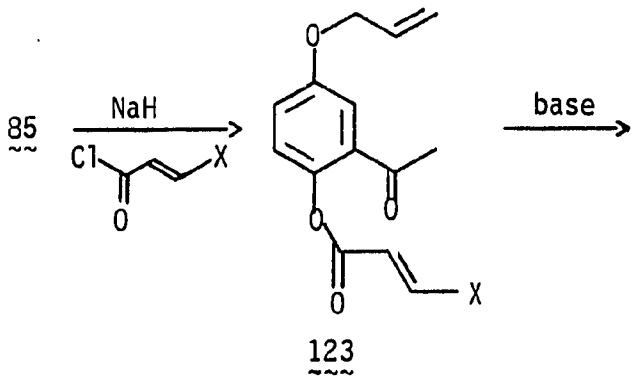
121



122

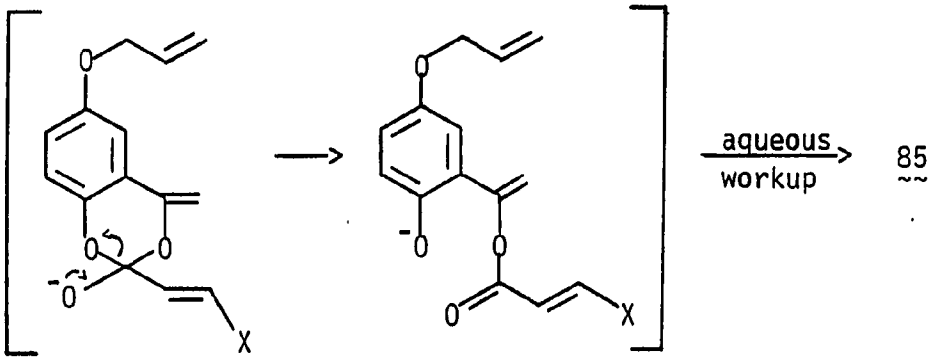
The problem here undoubtedly lies in the acyl transfer step, since the intermediate aryl esters (e.g., 123) from the sodium hydride step could be isolated in high yield. However, no recognizable desired products were obtained after addition of the potassium t-butoxide-t-butanol complex. Various attempts to produce β-diketones using different bases (LDA, KH, LiTMP, NaOMe/MeOH) at -78° proved to be unsuccessful. In every case, the starting o-hydroxy ketone 85 was recovered in high yield from the reaction mixture.

Presumably, electron withdrawing groups in the β-position make the carbonyl group of the phenol ester 123 more electrophilic. Intramolecular O-acylation of the ketone enolate might then occur. The resulting enol ester would likely be cleaved by the aqueous work-up. A rationale for the recovery of starting material in the cases of the acid chlorides with electron donating groups at the β-position is not obvious.

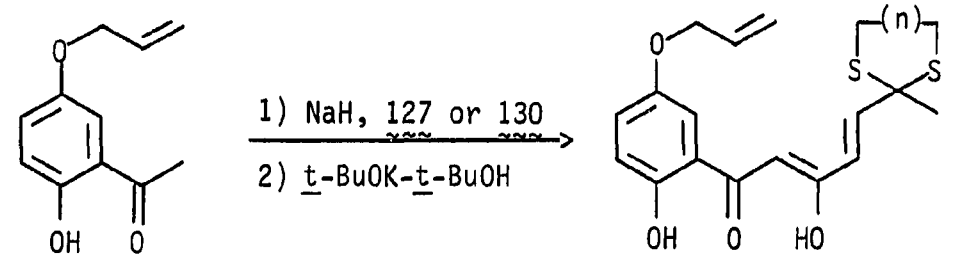


123

X = Electron Withdrawing Group

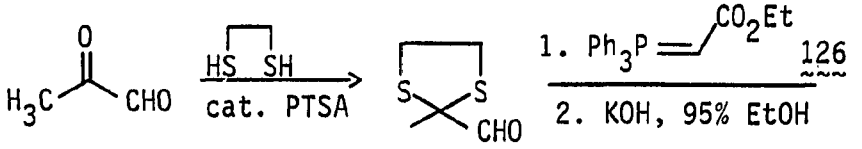


The results described above were disappointing, since we believed that the expected β-diketones would be very useful precursors for our synthesis of 11-deoxyanthracyclines and related antitumor antibiotics. Fortunately, it was discovered that the acyl transfer reactions of 85 with acid chlorides 128 and 130 bearing the thioketal moiety in the β-position proceeded cleanly to yield the desired β-diketones 116 and 117 in good yield. We considered these compounds as viable precursors to 11-deoxydaunomycinone since they contained the latent acetyl side chain. The requisite acid chloride 128 could be prepared in four steps from

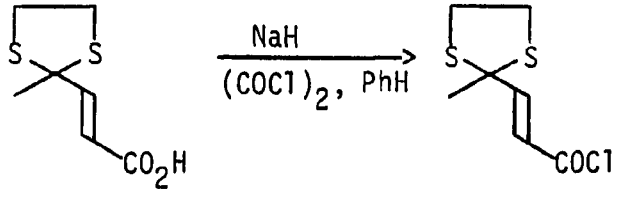


85

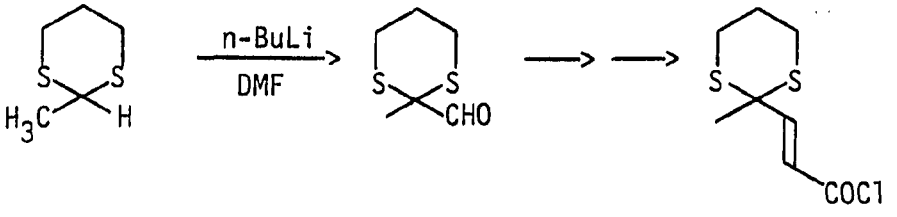
116: n = 0 76%
117: n = 1 72%



124 125



127 128



129 130

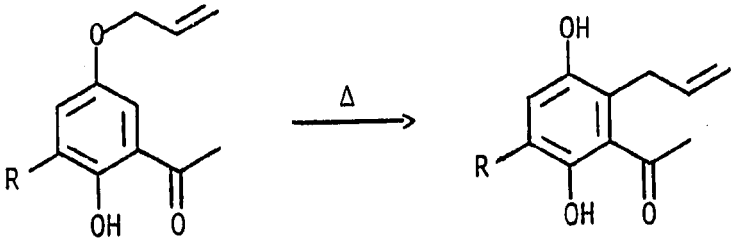
aqueous pyruvaldehyde 124.[72] Using a similar sequence, conversion of 129 to 130 was accomplished in good overall yield.

Notwithstanding some limitations, the one-pot procedure developed here represents a viable, convenient method for the synthesis of various types of β-diketones and will become a useful alternative to existing intermolecular pathways. In view of variable yields obtained in the traditional Baker-Venkataraman reaction, this modification should furnish higher yields and permits its extension to more elaborate and sensitive flavones.

In connection to our program aimed at developing new approaches to anthracycline antibiotics, the chemistry described herein allowed us to test the viability of our strategy. With several easily prepared β-diketones in hand, we directed our attention toward the crucial tandem Claisen-Diels-Alder reaction.

Tandem Claisen-Diels-Alder reactions

The rearrangement of allyl phenyl ethers to O-allyl-phenols, termed the Claisen rearrangement, has been less often used in organic synthesis than its aliphatic counterpart.[73] A major drawback of this reaction is the formation of a mixture of regioisomers when unsymmetrical systems are employed. For example, both m-methylphenyl and m-methoxyphenyl allyl ether afford approximately equal amounts of isomeric products, yet certain m-acyl groups exert a pronounced directing effect.[74] In particular, it is known that 2-hydroxy-5-allyloxyacetophenone 85 undergoes a regioselective Claisen rearrangement to produce 2,5-dihydroxy-6-allylacetophenone 131.[75]



85: R = H
132: R = SPh

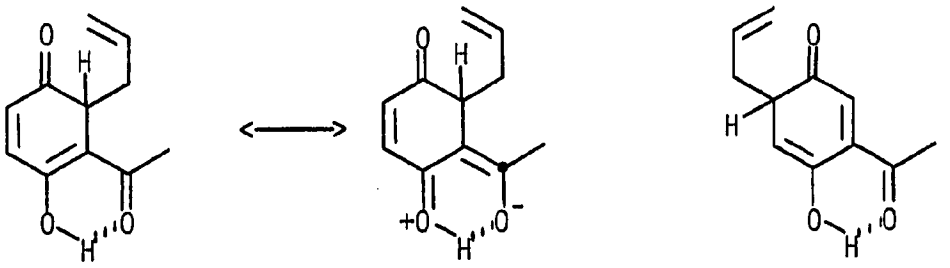
131: R = H
133: R = SPh

Recently, we have found that Claisen rearrangement of 132 also proceeds regioselectively to give hydroquinone 133. It is interesting to note that if the phenol is protected as either the methyl ether or the acetate, the Claisen produces approximately a 6:4 ratio of isomeric products.[75]

In view of these results, the hydrogen bonding between the phenolic hydrogen and the acetyl oxygen atom resulting in a six-membered chelate ring seems to be a dominant factor in controlling the Claisen selectivity. We feel that the protection of the phenol forces the acyl group out of plane of the aromatic ring, thus diminishing its directing effect. However, the origin of the excellent regioselectivity of the Claisen rearrangement when an acyl group is present in the meta position has not yet been defined.

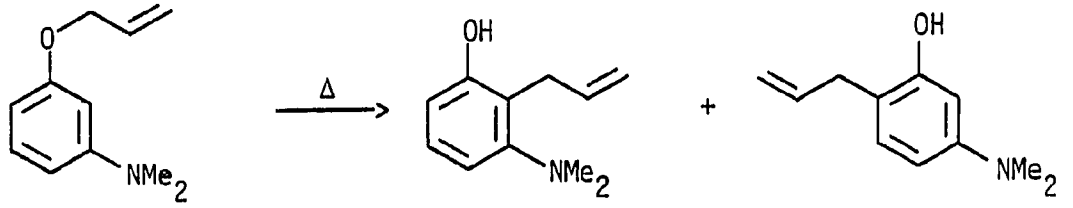
Recently, Kruse and Cha have noted that comparing the relative stability of the valence-bond resonance forms before aromatization can explain the Claisen selectivity.[76] They suggested that o-hydroxy ketone 85 rearranged preferentially by a transition state resembling A

which maintains resonance stabilization through four conjugated π-bonds, rather than B wherein only three π-bonds are directly conjugated.



A B

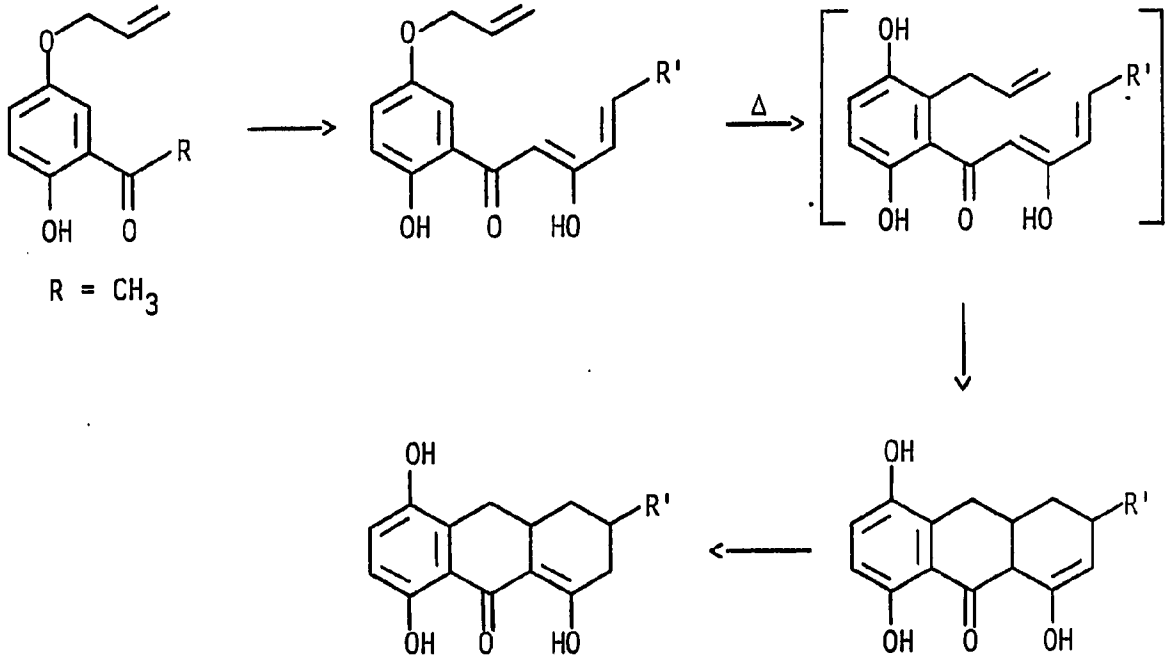
Although this argument may hold for the case at hand, we have not been able to identify other regioselective Claisen rearrangements by applying this rationale. For example, a dimethylamino group would be predicted to show a preference. In fact, it gives almost equal amounts of the two Claisen rearrangement products.



Our efforts at constructing a linearly fused tricyclic system by coupling the Claisen rearrangement with an intramolecular Diels-Alder reaction required a diene unit R (Scheme 2). The β-diketones 36, 102-104, 108, 109 and 115~117, prepared previously by a modification of the Baker-Venkataraman reaction, contain a 1-acyl-2-hydroxybutadiene subunit as a diene component. The dienophile component of the Diels-Alder reaction arises from the regioselective Claisen rearrangement. It

is noteworthy that no intermolecular Diels-Alder reaction for such dienes appears to be known and only one intramolecular example has been reported.[77]

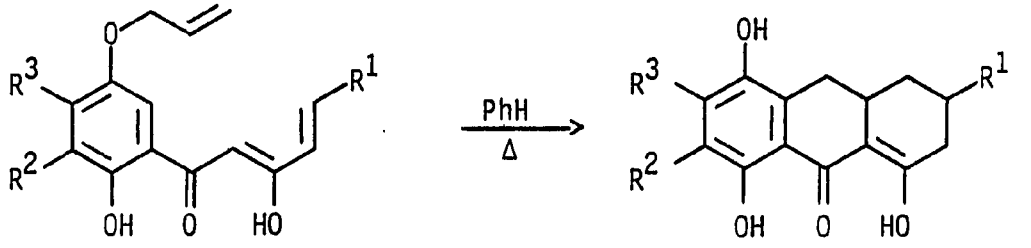
Scheme 2

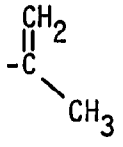
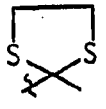
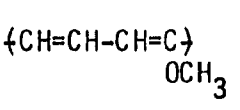
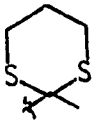
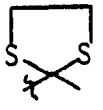


As noted previously, we believed that a prerequisite for successful anthracycline synthesis was the identification of a suitable group for R^1 (Scheme 2). This group must be compatible with the conditions of the tandem Claisen-Diels-Alder reaction and must be readily elaborated to the side chain of the A ring. In order to define a range of usable groups for R^1, several β-diketones 86, 102-104, 108, 109, and 115-117 were thermolyzed. The results of this study are listed in Table 2.

Qualitatively, the rate-determining step of the tandem Claisen-Diels-Alder reaction appears to be the Claisen rearrangement step. This is

Table 2. Tandem Claisen-Diels-Alder reaction of β-diketones



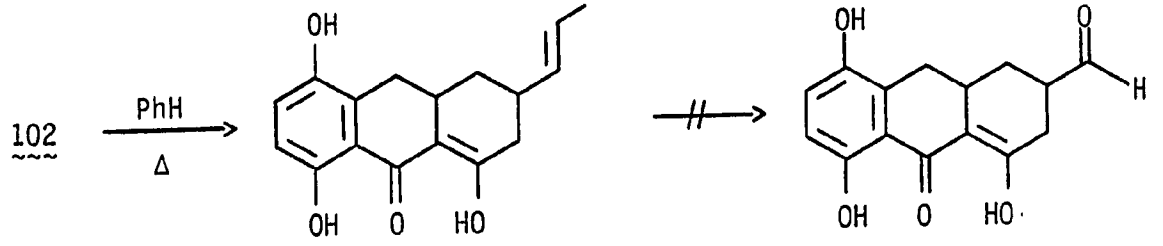
Entry	R_1	R_2	R_3	(β-Diketone)	Conditions	Yield	Product
1	$-CH_3$	H	H	86	210°/12 hr	84%	134
2	$-CH=CH-CH_3$	H	H	102	210°/12 hr	70%	135
3		H	H	103	210°	-	-
4	$-CH=CH_2$	H	H	104	230°/14 hr	10%	136
5	$-CH=CH-CH_3$	H	OCH_3	108	210°/10 hr	100%	137
6				109	250°	-	-
7	-SØ	H	OCH_3	115	210°	-	-
8		H	H	116	240°/18 hr	85%	138
9		H	H	117	240°/24 hr	81%	139
10	CH_3	SPh	H	140[a]	230°/18 hr	68%	141

[a]Preparation of 140 is detailed in Part II.

based solely on the fact that none of the intermediate Claisen products could be isolated by stopping the reaction before completion.

Entries 1 and 10 depict reactions which yield interesting tricyclic β-diketones, 134 and 141; a recognizable unit of the CBA ring portion of nogalomycin. A further study utilizing these compounds for the synthesis of nogalamycin will be detailed in Part II.

For the synthesis of 11-deoxydaunomycinone, we initially explored the use of tricyclic β-diketone 135 as an intermediate. An advantage of this choice is that the acid chloride of commercially available sorbic acid could be used in the acyl transfer step. Although both the acyl transfer reaction and tandem Claisen-Diels-Alder reaction worked well, a preliminary study showed that the propenyl group on 135 could not be reproducibly oxidized to the corresponding carboxaldehyde 142 under a variety of conditions.

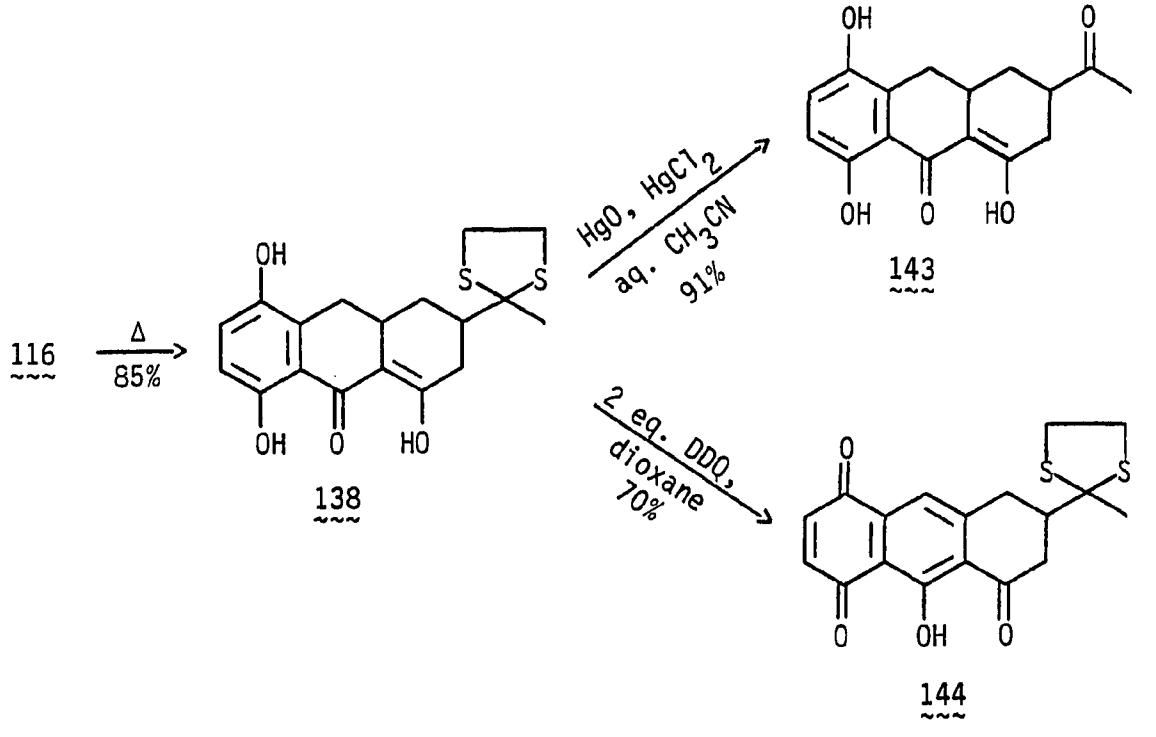


135 142

To our delight, it was found that β-diketone 116 bearing the thioketal moiety proceeded smoothly via a tandem Claisen-Diels-Alder reaction to afford the desired tricyclic β-diketone 138 as a 3:1 mixture of diastereomers in 85% yield. For our particular study, the relative

stereochemistry at the ring junction is not important, since only one of the stereogenic centers remains after the next step.

Subsequent dethioketalization under standard conditions ($HgCl_2$, HgO, aqueous CH_3CN) allowed formation of the interesting tricyclic ketone 143 as a yellow crystalline solid in 91% yield after chromatography on silica gel.

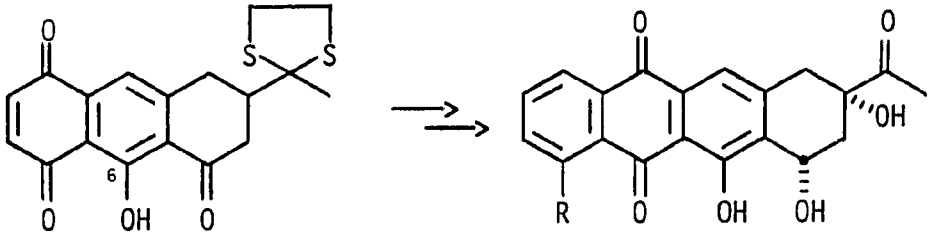


A direct oxidation of 138 to naphthoquinone 144 could be achieved using two equivalents of 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) in dioxane at ambient temperature. It is worth pointing out that the choice of the eluent (CH_2Cl_2) during chromatography is very crucial for isolating quinone 144 in highly pure form from the byproduct (H_2DDQ), which has polarity very similar to that of 144. Use of other solvent

variations such as hexane-ether or hexane-ethyl acetate is ineffective and results in a low yield of quinone 144.

Synthesis of 11-deoxydaunomycinone and its 4-demethoxy analogue

Naphthoquinone 144 contains functionality well suited for the synthesis of 11-deoxyanthracyclinones with different D ring substitution patterns. It already possesses the requisite B and C ring functionality and latent acetyl side chain of the A ring. Since Keay and Rodrigo[78] have shown that the hydroxy group at C-9 could be introduced by hydroxylation of a ketone enolate, naphthoquinone 144 is a viable precursor to 11-deoxydaunomycinone 145 and its 4-demethoxy analogue 146.



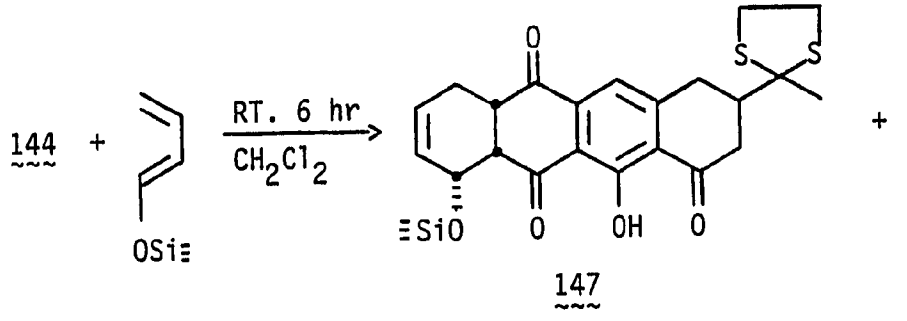
144

145: R = OCH_3

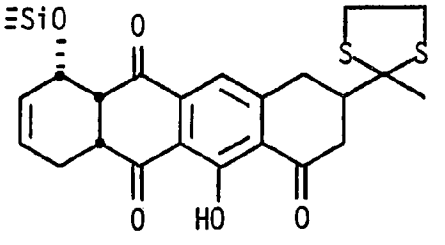
146: R = H

With a CBA ring synthon 144 available, our attention was focused on the crucial Diels-Alder reaction that would append the D ring. As mentioned previously, cycloaddition of 144 with a polarized diene was anticipated to occur with high regioselectivity. This expectation was based upon ample literature precedents wherein Diels-Alder reactions of 5-hydroxy-1,4-naphthoquinones were shown to be highly regioselective.[53-57]

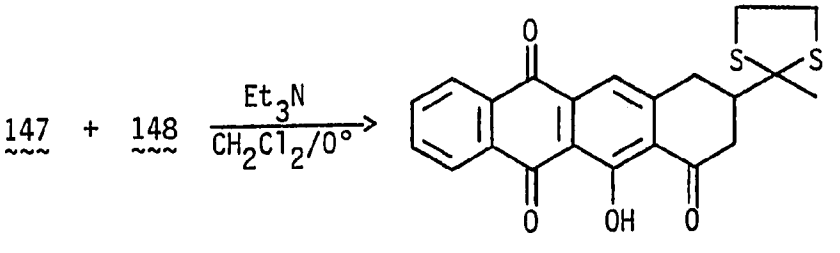
Initially, we examined the Diels-Alder reaction of ~~144~~ with 1-trimethylsilyloxy-1,3-butadiene. The reaction of ~~144~~ with 1-trimethylsilyloxy-1,3-butadiene proceeded smoothly at room temperature, but produced a 4:3 ratio of two regioisomeric adducts ~~147~~ and ~~148~~. A 300 MHz proton NMR of the crude reaction product obtained in quantitative yield revealed two sharp singlets at -0.275 ppm and -0.278 ppm for the trimethylsilyloxy group, thus indicating that both adducts ~~147~~ and ~~148~~ were "endo" isomers.



147



148



149 69% from 144

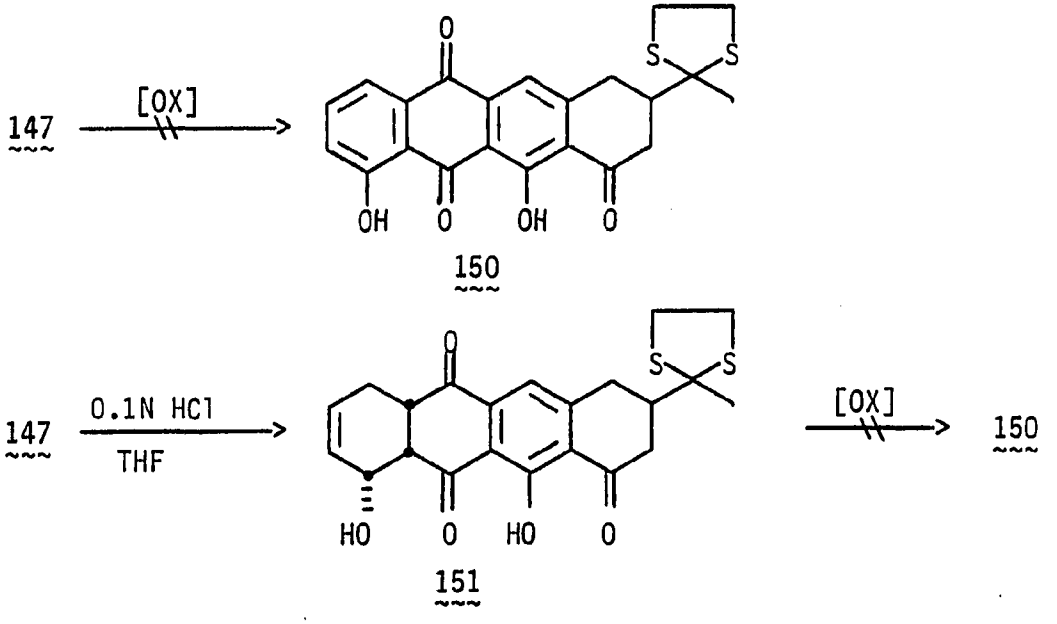
Contrary to our expectation, the directing effect of the hydroxyl group at C-6 is diminished in comparison to 5-hydroxy-1,4-naphthoquinone. It is likely that preferential hydrogen bonding with the benzylic ketone at C-7 is attenuating the directing effect.

For the synthesis of 4-demethoxy analogue ~~146~~ - a molecule which poses no regiochemical problem - both adducts could be used. Thus, a mixture of regioisomers 147 and 148 was treated with two equivalents of triethylamine at 0°C in methylene chloride to afford the aromatized tetracyclic anthraquinone 149 in 69% overall yield. Starting from 2-hydroxy-5-allyloxy-acetophenone 85, anthraquinone 149 was obtained in just five steps.

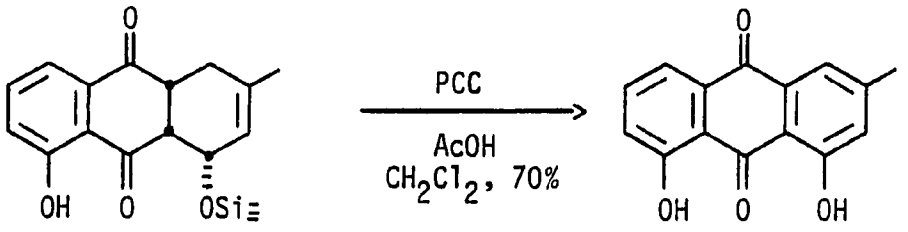
In order to overcome the lack of regiochemical control, we next examined the Diels-Alder behavior of quinone 144 in the presence of various Lewis acids. The ability of Lewis acids to enhance the regioselectivity in cycloadditions between unsymmetrical dienes and peri-hydroxyquinones is well documented.[79-81] In practice, however, selection of the specific Lewis acid employed in any particular reaction is usually based on trial and error or serendipitous experimentation.

Catalysis of the reaction of 144 and 1-trimethylsilyloxy-1,3-butadiene with boron trifluoride etherate (0.05 eq) at -20° in benzene led to immediate decomposition, while other Lewis acids such as $B(OAc)_3$ and $AlCl_3$ had little effect on the regioselectivity. However, when the Diels-Alder reaction was conducted with one equivalent of freshly fused zinc chloride at 0°C in CH_2Cl_2, one regioisomer was exclusively formed in a 50:1 ratio.

Oxidation of this product, tentatively identified as 147, with either Jones' reagent,[82] DDQ in benzene, trityl fluoroborate,[83] activated MnO_2 or PCC[84] in the presence of two equivalents of acetic acid afforded a complex mixture of products containing the desired hydroxyanthraquinone, a deoxyanthraquinone derived from loss of TMSOH, and other unidentified byproducts.

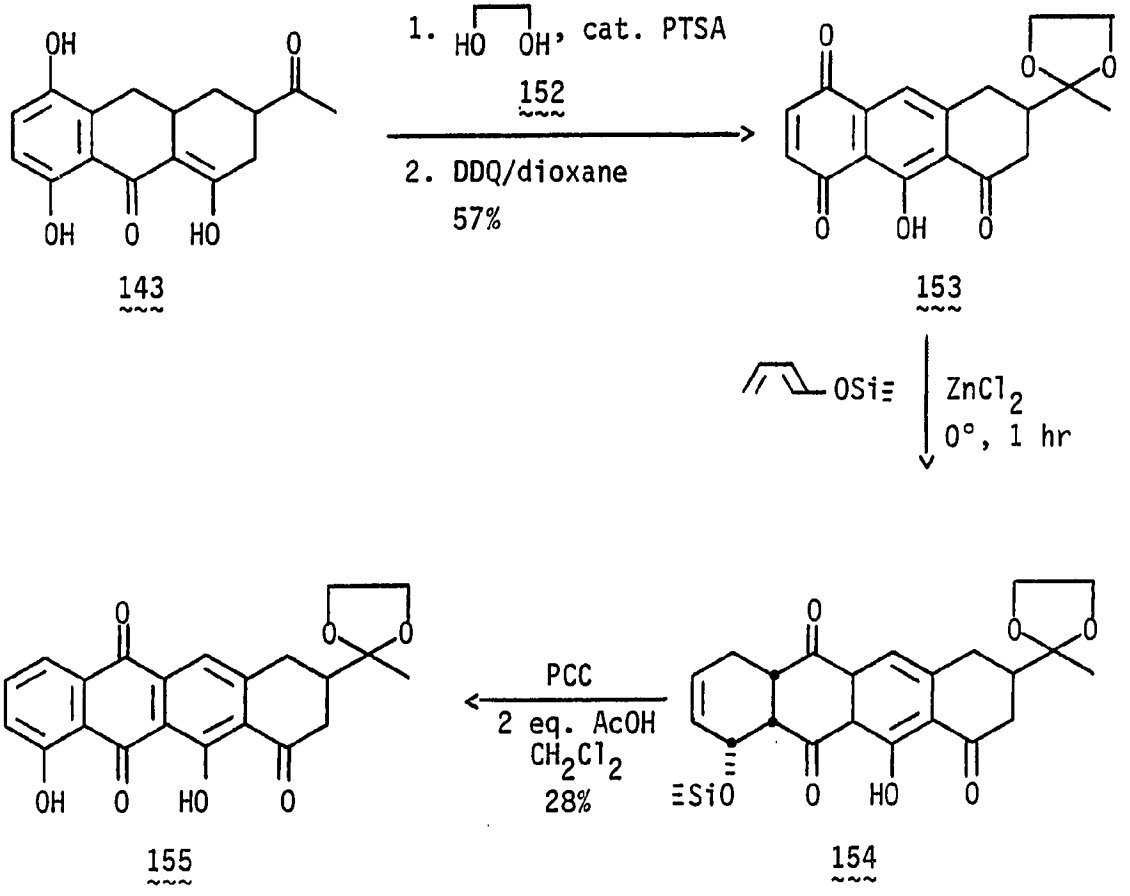


Since direct oxidation of silyl ether 147 proved to be difficult, it was hydrolyzed to the corresponding allylic alcohol 151 in excellent yield with 0.1N HCl in THF. Unfortunately, neither a Swern oxidation (oxalyl chloride, Et_3N, Me_2SO), a Collins oxidation nor an oxidation with buffered PCC provided any of the desired hydroxyanthraquinone 150. These results were in contrast to the analogous oxidation of the Diels-Alder adduct reported by Krohn and coworkers,[84] as shown below.



Surmising that part of the difficulties in inducing aromatization came from the presence of the thioketal moiety, we proceeded to prepare Diels-Alder adduct 154 with the dioxolane group starting from 143 as outlined in Scheme 3. However, treatment of 154 with PCC in the presence

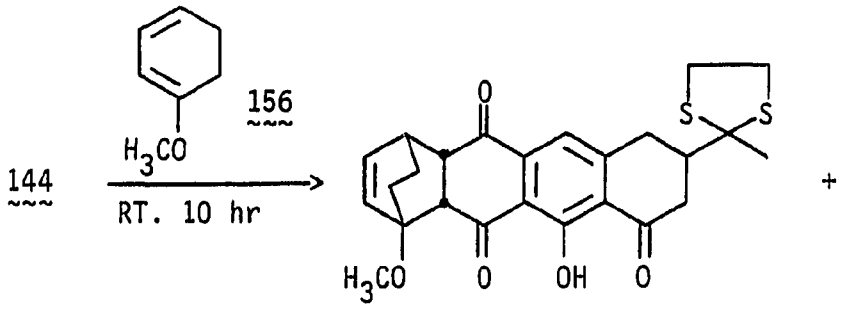
Scheme 3



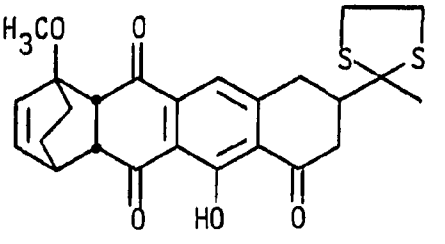
of two equivalents of acetic acid produced a very poor yield (28%) of the desired hydroxyanthraquinone 155. Thus, despite the investment of a a substantial amount of effort to use 1-trimethylsilyloxy-1,3-butadiene as the D ring precursor, we were forced to abandon it.

In those reactions that exhibited high regiocontrol with 5-hydroxy-1,4-naphthoquinone, the diene components were always significantly polarized, electron rich, and terminally substituted with a good π-electron donating substituent. Consequently, the next diene examined was 1-ethoxy-1-trimethylsilyloxy-1,3-butadiene. Somewhat surprisingly, a Diels-Alder reaction of quinone 144 with this ketene acetal failed to afford any of the desired adduct and resulted in intractable tars at room temperature. Identical observations were made when the diene was added to a solution of the quinone 144 at -78°C. Independent results from these laboratories indicate that electron transfer or an ionic pathway intervenes in the cycloaddition of 1-ethoxy-1-trimethylsilyloxy-1,3-butadiene with activated quinones.

As a possible solution to this problem, we next considered 1-methoxy-1,3-cyclohexadiene as a diene for the construction of the D ring. A favorable aspect of this diene is that the requisite methoxyl group can be introduced directly. The Diels-Alder reaction of quinone 144 with 1-methoxy-1,3-cyclohexadiene 156 proceeded smoothly at room temperature in methylene chloride to provide a 1.8:1 mixture of adducts 157 and 158.



157



158

In order to enhance the regioselectivity, Lewis acid-catalyzed cycloaddition of 144 and 156 was then examined. In contrast to the findings observed previously, the zinc chloride (one equivalent) - catalyzed reaction of 144 and 156 resulted in a complex mixture of products. With 0.3 equivalent of zinc chloride, the regioselectivity of this reaction could be improved, but the yield remained low. Several other Lewis acids were examined, such as $BF_3 \cdot Et_2O$, $B(OAc)_3$, $AlCl_3$, and Et_2AlCl, had little effect on the regiochemical outcome or led to a number of unidentified products with overall poor mass balance (Table 3).

We were pleased to find that the ratio of Diels-Alder adducts 157 and 158 was also affected by solvent polarity. As shown in Table 3, with DMSO as solvent, a 6.7:1 ratio of 157 to 158 could be achieved. This

Table 3. Diels-Alder reaction of 144 and 156

Lewis acid[a] (equiv, temp)	The ratio of 157 to 158
$ZnCl_2$ (0.3, 0°)	20:1[b]
$ZnCl_2$ (1.0, 0°)	-
$BF_3 \cdot Et_2O$ (0.1, -20°)	-
$B(OAc)_3$ (1.2, 20°)	3.4:1
$AlCl_3$ (1.0, -78°)	-
Et_2AlCl (1.0, -20°)	1.7:1

Solvent[c]	The ratio of 157 to 158
CH_2Cl_2	1.8:1
THF	2.2:1
toluene	3:1
PhH	3.1:1
DMF	5.4:1
DMSO	6.7:1

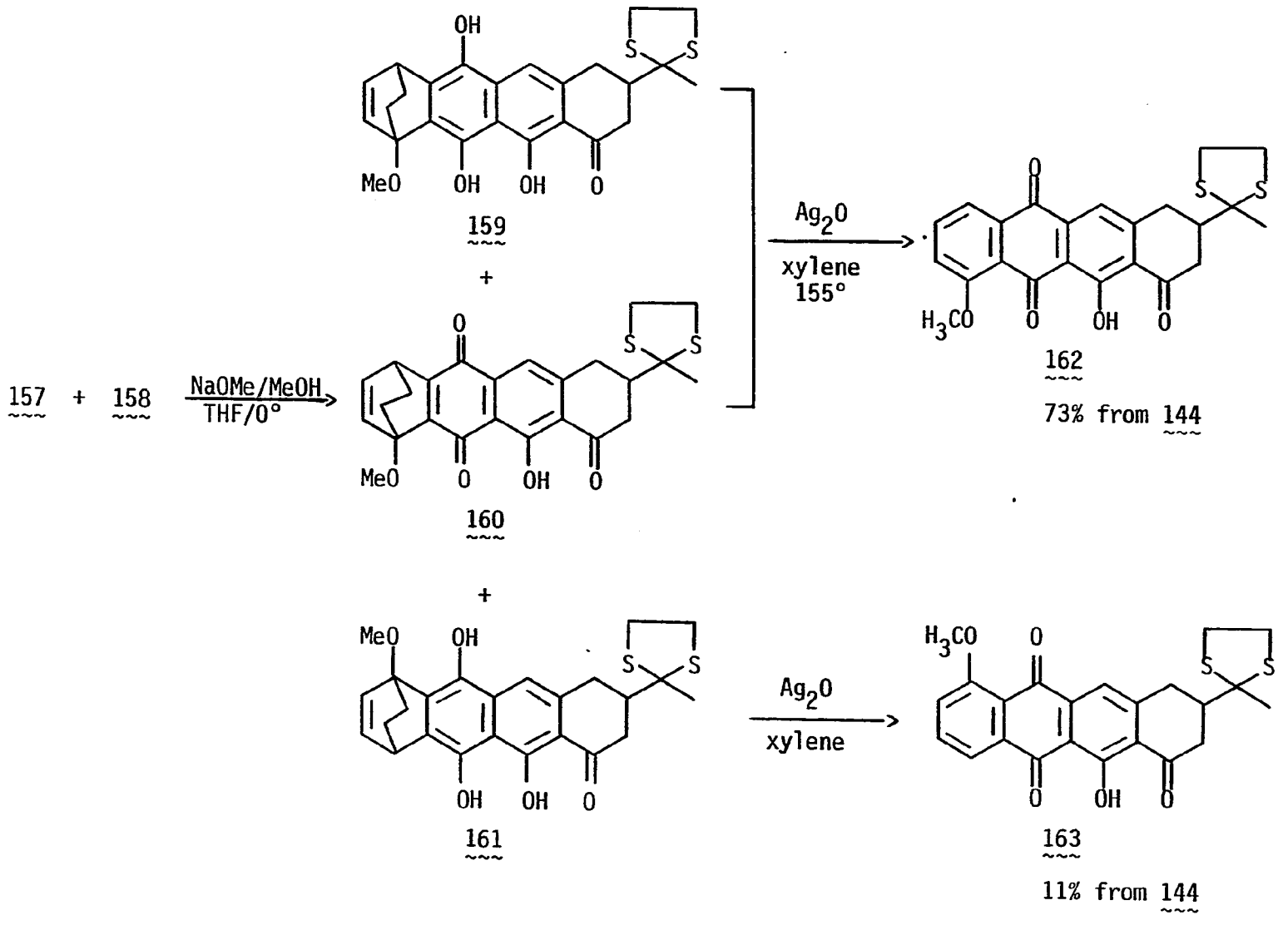
[a]All Lewis-acid catalyzed reactions were performed in a methylene chloride solvent.

[b]Low yield.

[c]Reaction was carried out at room temperature.

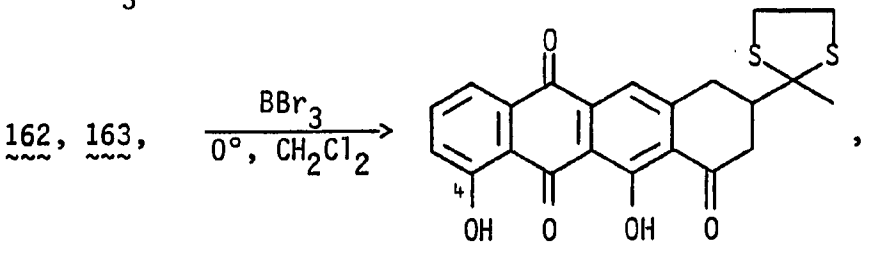
solvent effect is surprising and may arise from the disruption of internal hydrogen bonding by the polar solvent. This result demonstrates, for the first time, that it is possible to alter substantially the regioselectivity of cycloaddition of peri-hydroxyquinones by the choice of the solvent.

Although several methods for annulating aromatic rings onto quinones have been reported,[85-88] finding conditions for efficient aromatization of Diels-Alder adducts proved to be much more difficult than we originally anticipated. After much experimentation, successful preparation of anthraquinone 162 was accomplished in excellent yield using a modification of a literature procedure.[88] Enolization of a mixture of adducts 157 and 158 with sodium methoxide in THF at 0°C followed by acid work-up (glacial CH_3COOH) produced the expected hydroquinones 159 and 161, along with the quinone 160. It is conceivable that quinone 160 can be derived from the corresponding hydroquinone 159 by air-oxidation. These three compounds were readily separable, and could be distinguished by their NMR spectra. The desired hydroquinone 159 and quinone 160 were subsequently pyrolyzed in xylene at 155°C in the presence of silver(I) oxide to afford the 4-methoxyanthraquinone 162 with expulsion of ethylene. The overall yield of 162 from tricyclic quinone 144 was 73% yield. Using the same conditions, the minor component 161 could be converted into anthraquinone 163.

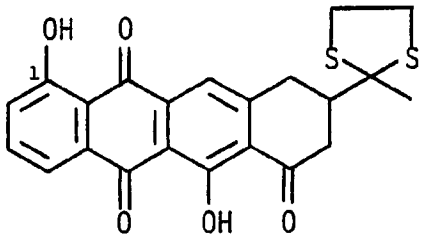

157 + 158
NaOMe/MeOH
THF/0°
159
+
160
+
161
Ag2O
xylene
155°
Ag2O
xylene
162
73% from 144
163
11% from 144

The anthraquinones 162 and 163 thus obtained are nearly identical by NMR and IR. They differ most noticeably in the chemical shift of their chelated phenolic protons. For anthraquinone 163, this proton appears as a sharp singlet at 13.86 ppm. The peri-methoxyl group strengthens the chelation effect in 162, causing a 0.28 ppm downfield shift to 14.14 ppm for anthraquinone 162.

In order to obtain additional evidence for our structural assignments, both 162 and 163 were converted to their corresponding O-demethylated products 164 and 165, respectively, by treatment with one equivalent of BBr_3 at 0°C in methylene chloride. We reasoned that the



164

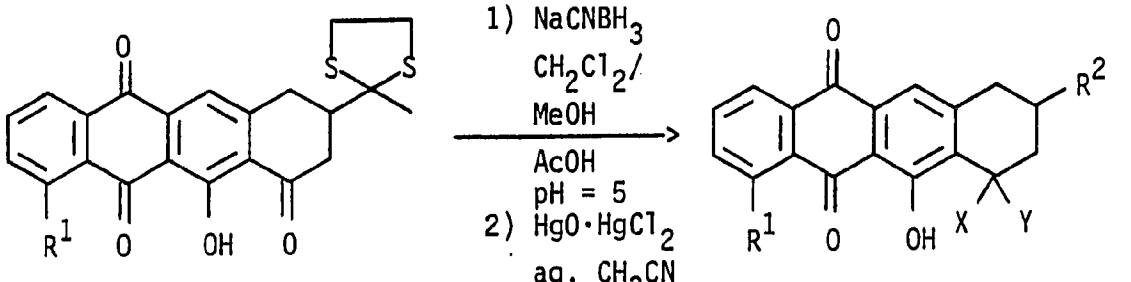


165

IR spectrum of 4-hydroxyanthraquinone 164 would show two distinct hydrogen-bonded and nonhydrogen-bonded quinone carbonyl peaks, thus confirming that both phenols are chelated to the same carbonyl. On the other hand, 1-hydroxyanthraquinone 165 was anticipated to exhibit a single quinone carbonyl absorption around 1630 cm^{-1}, since both carbonyl

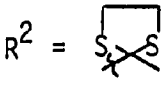
groups are chelated. In practice, however, 4-hydroxyanthraquinone 164 was indistinguishable from 165 by IR. Thus, the structure of 164 had to be confirmed unambiguously in the last step of our synthesis.

Having established the direct route to the tetracyclic framework of the anthracyclinone nucleus, we directed our attention toward the elaboration of the A ring functionality for completion of the synthesis of 11-deoxydaunomycinone and its 4-demethoxy analogue. Our initial attempts to reduce 149 to 166a with either $BH_3 \cdot Me_2S$ or $NaBH_4$ were unsuccessful and resulted in a complex mixture of unidentifiable products. We found that 149 could be reduced to 166a in good yield with sodium cyanoborohydride in CH_2Cl_2/MeOH containing acetic acid to maintain a pH of 5. Subsequent dethioketalization was effected by treatment with $HgCl_2$ and HgO at room temperature in aqueous acetonitrile to afford 167a

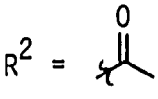


149: R^1 = H
162: R^2 = OCH_3

a: R^1 = H b: R^1 = OCH_3
166: X = OH, Y = H,

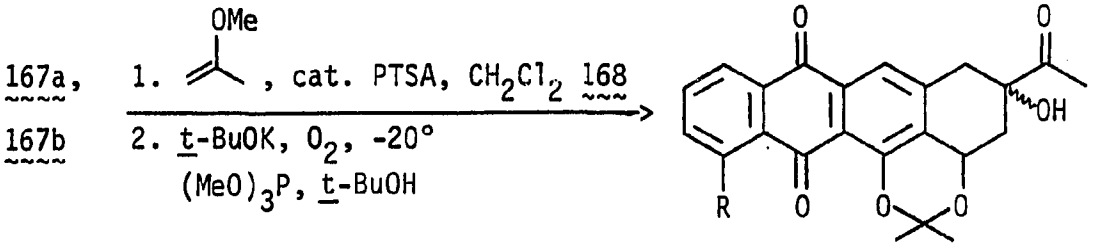


167: X = OH, Y = H,



in 89% yield. Using the same sequence, conversion of anthraquinone 162 to 167b were accomplished in good overall yield. The hydroxyketones 167b were present in a 10:1 ratio, with the major component being the cis isomer.

Subjecting 167a and 167b to ketalization with 2-methoxypropene containing catalytic amounts of p-toluenesulfonic acid in methylene chloride furnished the expected acetonides 168a and 168b, respectively, in good to excellent yield. The required tertiary hydroxy group at C-9 was then introduced via oxygenation of the ketone enolate using the method of Keay and Rodrigo[78] (t-BuOk, O_2, $P(OMe)_3$, THF/t-BuOH, -20°).

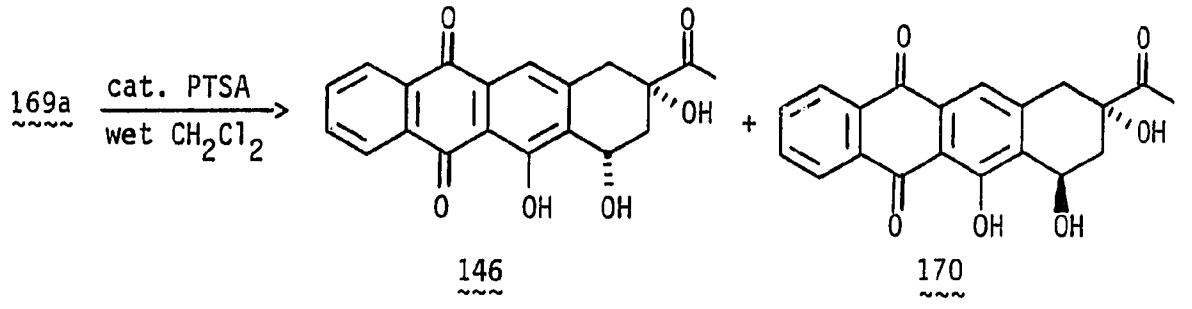


169

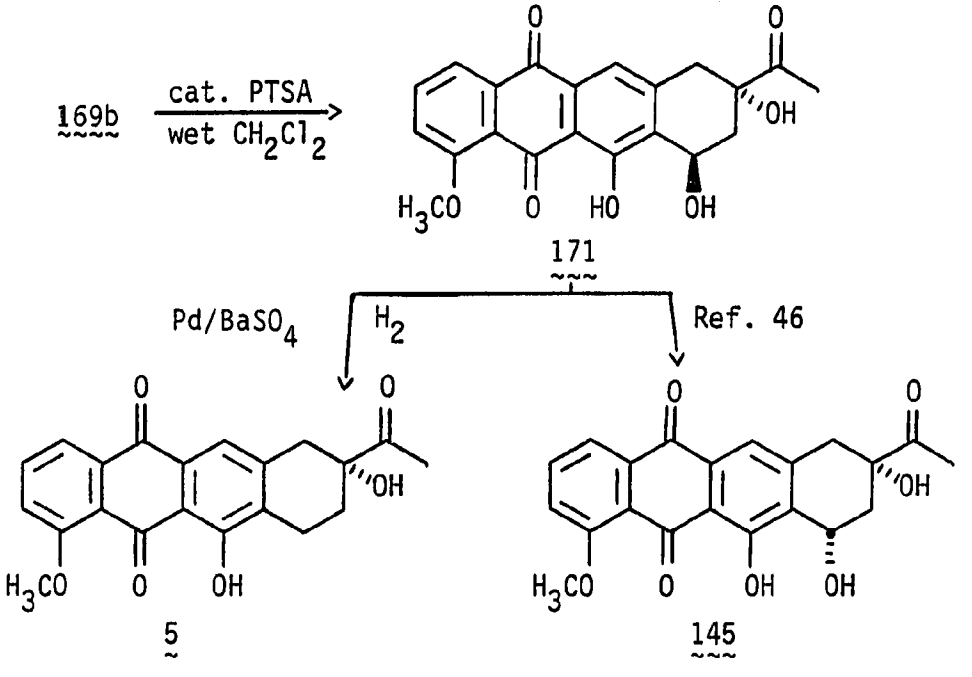
a: $R^1 = H$

b: $R^1 = OCH_3$

Hydrolysis of the acetonide 169a with p-toluenesulfonic acid in wet CH_2Cl_2 produced a 2:1 mixture of 4-demethoxy-11-deoxydaunomycine 146 and its epimer 170 which were readily separable by chromatography. The spectral data (NMR, IR) and the melting point of 146 thus obtained are in accord with those previously reported.[89] The epimerization of the C-7 epimer 171 to 146 was possible using literature procedures.[89]



Finally, the 4-methoxyanthraquinone 169b was subjected to the same deprotection conditions described above, affording the C-7 epimer 171 of 11-deoxydaunomycinone 145. The chemical structure and stereochemistry of 171 was confirmed unambiguously by its conversion into the known



7,11-dideoxydaunomycinone 5 via a catalytic hydrogenolysis ($Pd/BaSO_4$, H_2, EtOAc). The NMR and IR spectra of 5 were identical with those reported by others.[21,47] Since the C-7 epimer 171 has been previously isomerized

to 145 with trifluoroacetic acid,[46] the chemistry described above provides a direct route to racemic 11-deoxydaunomycinone in 11 steps starting from readily available 2-hydroxy-5-allyloxy-acetophenone.

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.

2,5-Dihydroxy-4-methoxyacetophenone (96)

To a stirred solution of 3.88 g (17.3 mmol) of 95 in 20 ml of glacial acetic acid at room temperature was added 2.5 ml (17.3 mmol) of $BF_3 \cdot Et_2O$. After refluxing for 1 hour, the solution was cooled to room temperature. A 15 ml solution of 5N HCl was then added and the reaction mixture was refluxed again for 30 minutes. The resulting dark solution was then poured into a mixture of ethyl acetate and water. The water layer was separated and extracted with ethyl acetate. The combined organic layer was washed with saturated brine, dried, and concentrated to afford the crude 96. This material was crystallized from absolute ethanol to afford 2.58 g (82%) of pure 96 as colorless plates: mp 167-168°C; 60 MHz ^1H NMR ($CDCl_3$) δ 2.45 (s, 3 H), 3.85 (s, 3 H), 6.34 (s, 1 H), 7.18 (s, 1 H), 12.53 (s, 1 H); IR (film) 3540, 2950, 1620, 1585, 1440, 1270, 1060, 950 cm^{-1}; high resolution spectrum for $C_9H_{10}O_4$ requires 182.05791, determined 182.05828.

5-Allyloxy-2-hydroxy-4-methoxyacetophenone (97)

To a stirred solution of 96 (2.50 g, 13.73 mmol) in acetone (20 ml) at room temperature was added anhydrous potassium carbonate (1.95 g, 13.73 mmol) followed by allyl bromide (1.22 ml, 13.8 mmol). The reaction mixture was heated at reflux for 8 hours. The reaction was diluted with water, acidified with 6N HCl to pH 5, and extracted with ethyl acetate. The extracts were combined, washed with brine, dried, and concentrated in

vacuo. The crude product was purified by chromatography on silica gel using 3:1 hexane: ethyl acetate to afford 2.11 g (69%) of 97: mp 96-96.5°C; 300 MHz ^{1}H NMR ($CDCl_3$) δ 2.52 (s, 3 H), 3.99 (s, 3 H), 4.74 (dd, 2 H, J = 5.4 Hz, J = 1.2 Hz), 5.31 (dd, 1 H, J = 10.5 Hz, J = 1.2 Hz), 5.44 (dd, 1 H, J = 16.8 Hz, J = 1.5 Hz), 6.01-6.15 (m, 1 H), 6.43 (s, 1 H), 7.13 (s, 1 H), 12.47 (s, 1 H); IR ($CDCl_3$) 3160, 2950, 1615, 1440, 1365, 1060, 985 cm^{-1}; ^{13}C NMR 26.12, 55.95, 71.20, 110.46, 111.66, 115.30, 117.94, 133.26, 140.39, 157.44, 160.18, 201.88 ppm; high resolution mass spectrum for $C_{12}H_{14}O_4$ requires 222.08921, determined 222.08916.

2-Acetyl-1,4-dihydroxy-8-methoxynaphthalene (99)

To a solution of phthalide 98 (2.15 g, 11.37 mmol) and methyl vinyl ketone (1.04 ml, 12.5 mmol) in 57 ml of dimethylsulfoxide at ambient temperature was added potassium tert-butoxide (1.945 g, 17.35 mmol). After stirring 90 minutes at room temperature an equal portion of potassium tert-butoxide was added and stirring continued for 2 hours. The reaction mixture was diluted with 30 ml of diethyl ether and acidified with excess 2N HCl. The resulting yellow solution was poured into 500 ml of ice water and extracted with diethyl ether (50 ml x 5). The organic extracts were combined, washed with brine, and dried. The solvents were removed in vacuo and the residue chromatographed on silica gel eluting 2.5:1 hexane:ethyl acetate to afford 1.74 g (66%) of 99: 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), 13.60 (s, 1 H); IR ($CDCl_3$) 3600-3400 (br), 1640, 1600, 1435, 1270 cm^{-1}.

2-Acetyl-4-allyloxy-1-hydroxy-8-methoxynaphthalene (100)

Following the same procedure as that used to prepare 97, compound 99 (0.82 g, 3.53 mmol) was converted to 100 with allyl bromide (0.34 ml, 3.90 mmol) and anhydrous potassium carbonate (0.50 g, 3.53 mmol) in 20 ml of acetone. The crude product was purified by flash chromatography using 4:1 hexane:ethyl acetate to afford 0.68 g (71%) of 100 as a yellow solid: mp 113-114°C; 300 MHz ^1H NMR ($CDCl_3$) δ 2.63 (s, 3 H), 4.10 (s, 3 H), 5.37 (d, 1 H, J = 10.3 Hz), 5.52 (dd, 1 H, J = 16.9 Hz, J = 1.2 Hz), 6.08-6.21 (m, 1 H), 6.93 (d, 1 H, J = 7.7 Hz), 6.99 (s, 1 H), 7.53 (t, 1 H, J = 8.0 Hz), 7.82 (d, 1 H, J = 8.1 Hz), 13.61 (s, 1 H); IR ($CDCl_3$) 3350, 2935, 1615, 1570, 1400, 1385, 1260, 1055 cm^{-1}; ^{13}C NMR 22.44, 50.24, 63.44, 98.44, 107.65, 108.74, 110.54, 111.27, 123.77, 126.62, 127.27, 139.56, 151.95, 153.02, 195.83 ppm.

4-Oxo-2-pentenoyl Chloride, Ethanedithioketal (128)

A solution of the ethanedithioketal of pyruvaldehyde (3.00 g, 20 mmol) and carboethoxymethylenetriphenylphosphorane (7.05 g, 20 mmol) in 30 ml of methylene chloride was heated at reflux for 8 hours. The solvent was removed *in vacuo*. After ether was added the resulting precipitate (Ph_3PO) was filtered off. The filtrate was concentrated and the residue chromatographed on silica gel using 8:1 hexane:ether to afford 4.02 g (91%) of 126 as a light yellow oil; 60 MHz ^1H NMR ($CDCl_3$) δ 1.33 (t, 3 H, 8 Hz), 1.95 (s, 3 H), 3.41 (br s, 4 H), 4.28 (q, 2 H), 5.93

(d, 1 H, J = 16 Hz), 7.17 (d, 1 H, J = 16 Hz); IR (film) 2980, 1730, 1645, 1260, 1160, 1030, 970 cm^{-1}. This product was hydrolyzed with 1.3 equiv of KOH in 95% ethanol (30 ml) at room temperature for 6 hours to afford a crude acid 127 which was taken directly on to the acid chloride. To a suspension of hexane-washed NaH (0.66 g, 13.7 mmol) in dry benzene (20 ml) at 5°C was added the crude acid 127 in 15 ml of benzene. Oxalyl chloride (1.30 ml, 15 mmol) was then added slowly and the solution was allowed to warm to room temperature over 1 hour. After stirring at ambient temperature for 3 hours, the resulting suspension was filtered and washed with benzene. The filtrate and washed was concentrated *in vacuo* and the residue purified by vacuum distillation (110°-115°/5 mmHg) to afford 2.98 g (81%) of 128 as a light yellow oil; 60 MHz ^1H NMR ($CDCl_3$) δ 1.93 (s, 3 H), 3.38 (br s, 4 H), 6.12 (d, 1 H, J = 16 Hz), 7.22 (d, 1 H, J = 16 Hz); IR (film) 3040, 1750, 1602, 1268, 1115, 1015, 960, 770 cm^{-1}.

4-Oxo-2-pentenoyl Chloride, Propanedithioketal (130)

Using the same procedure described above for 127, the acid chloride 130 was prepared starting with 129 in 69% overall yield: bp 105-110°C/4.5 mmHg; 60 MHz ^1H NMR ($CDCl_3$) δ 1.81 (s, 3 H), 2.05-2.42 (m, 2 H), 2.71-3.33 (m, 4 H), 6.28 (d, 1 H, J = 17 Hz), 7.28 (d, 1 H, J = 17 Hz); IR (film) 2950, 1760, 1610, 1420, 1250, 1110, 1020, 965, 760 cm^{-1}.

General Procedure for the Acyl Transfer Reaction

To a suspension of hexane-wash NaH (1.1 equiv) in dry THF (1 ml/mmol) at 0°C was added by syringe a solution of the requisite o-hydroxy

acetophenone (1 equiv) in THF. The resulting solution was stirred for 10 minutes at 0°C. The acid chloride (1.05 equiv) was then added dropwise and the solution was stirred at 0°C for 20 minutes. The potassium tert-butoxide/ tert-butanol complex (2.1 equiv) was then added in one portion. The deep red solution was stirred for 1 hour at 0°C. The reaction mixture was poured into ice water, acidified with 6N HCl to pH 6 and extracted with ethyl acetate. The organic extracts were combined, washed with brine, dried, and concentrated in vacuo. The crude product was purified by flash chromatography on silica gel using hexane and ethyl acetate as the eluent.

3-Hydroxy-1-[5-(allyloxy)-2-hydroxyphenyl]-hexa-2,4-diene-1-one (86)

Mp 108-108.5°C; 300 MHz ^{1}H NMR ($CDCl_3$) δ 1.96 (dd, 3 H, J = 6.9 Hz, J = 1.6 Hz), 4.50 (dd, 1 H, J = 5.1 Hz, J = 1.2 Hz), 5.30 (ddd, 1 H, J = 10.2 Hz, J = 3.6 Hz, J = 1.2 Hz), 5.42 (ddd, 1 H, J = 16.8 Hz, J = 2.7 Hz, J = 1.2 Hz), 6.05 (s, 1 H), 5.97 (d, 1 H, J = 15.6 Hz), 5.93-6.12 (m, 1 H), 6.96 (d, 1 H, J = 15.6 Hz), 6.81-7.32 (m, 3 H), 11.78 (s, 1 H), 14.67 (s, 1 H); IR ($CDCl_3$) 3200-2750 (br), 1640, 1560, 1470, 1320, 1280, 1200, 1180, 950, 830 cm^{-1}; ^{13}C NMR 12.48, 63.79, 89.09, 106.96, 111.64, 112.57, 113.25, 117.96, 120.34, 127.17, 134.00, 144.73, 150.82, 168.92, 189.55 ppm; MS m/e 69, 135, 192, 219, 260 (M+); high resolution mass spectrum for $C_{15}H_{16}O_4$ requires 260.10486, determined 260.10483.

3-Hydroxy-1-[5-(allyloxy)-2-hydroxyphenyl]-
octa-2,4,6-trien-1-one (102)

Mp 126-126.5°; 300 MHz ^{1}H NMR $CDCl_3$) δ 1.89 (d, 3 H, J = 6.1 Hz), 4.51 (d, 2 H, J = 5.30 Hz), 5.30 (d, 1 H, J = 10.4 Hz), 5.12 (dd, 1 H, J = 17.5 Hz, J = 1.1 Hz), 5.93 (d, 1 H, J = 15.2 Hz), 6.01-6.08 (m, 1 H), 6.10 (s, 1 H), 6.18-6.24 (m, 2 H), 6.90 (d, 1 H, J = 8.9 Hz), 7.08 (dd, 1 H, J = 8.9 Hz), 7.2 (d, 1 H, J = 2.8 Hz), 7.20-7.30 (m, 1 H), 11.82 (s, 1 H), 14.66 (s, 1 H); IR ($CDCl_3$) 3200-2850 (br), 1615, 1530, 1470, 1420, 1250 cm^{-1}; ^{13}C NMR δ 18.66, 70.17, 96.30, 113.48, 117.64, 119.01, 119.46, 123.43, 124.14, 130.71, 133.57, 138.97, 140.79, 151.07, 157.18, 175.65, 195.29 ppm; Elemental anal. Calcd for $C_{17}H_{18}O_4$: C, 71.31; H, 6.34. Found: C, 71.52; H, 6.48.

3-Hydroxy-1-[5-(allyloxy)-2-hydroxyphenyl]-
6-methylhepta-2,4,6-trien-1-one (103)

60 MHz ^{1}H NMR ($CDCl_3$) δ 1.91 (s, 3 H), 4.42 (d, 2 H, J = 7.1 Hz), 5.10-6.22 (m, 7 H), 6.71-7.55 (m, 4 H); IR (film) 3240-2830 (br) 1640, 1593, 1470, 1320, 1170, 950 cm^{-1}.

3-Hydroxy-1-[5-(allyloxy)-2-hydroxyphenyl]-
hepta-2,4,6-trien-1-one (104)

Mp 111-113°C; 300 MHz ^{1}H NMR ($CDCl_3$) δ 4.51 (d, 2 H, J = 5.1 Hz), 5.21-6.23 (m, 7 H), 6.11 (s, 1 H), 6.41-7.47 (m, 6 H), 11.78 (s, 1 H), 14.51 (s, 1 H); IR ($CDCl_3$) 3130-2830 (br) 1630, 1610, 1555, 1473, 1280, 1175, 1000, 955 cm^{-1}; ^{13}C NMR δ 69.83, 96.80, 108.87, 112.97, 117.70, 118.59, 119.33, 124.18, 124.87, 126.24, 133.15, 135.27, 140.19, 150.73,

156.96, 174.28, 195.45 ppm; high resolution mass spectrum for $C_{16}H_{16}O_4$ requires 272.10486, determined 272.10419.

3-Hydroxy-1-[5-(allyloxy)-2-hydroxyphenyl]-3-(4-methoxyphenyl)prop-2-en-1-one (105)

Mp 63-64°C; 300 MHz ^1H NMR ($CDCl_3$) δ 3.93 (s, 3 H), 4.48 (dd, 2 H, J = 5.1 Hz J = 1.2 Hz), 5.31 (dd, 1 H, J = 10.3 Hz, J = 3.7 Hz), 5.47 (dd, 1 H, J = 16.8 Hz, J = 2.8 Hz), 5.70-6.31 (m, 1 H), 6.71 (s, 1 H), 6.92-8.27 (m, 7 H), 11.63 (s, 1 H), 15.83 (s, 1 H); IR ($CDCl_3$) 2970, 1720, 1610, 1570, 1480, 1275, 1195, 1040 cm^{-1}; ^{13}C NMR δ 49.43, 63.91, 84.97, 107.37, 108.08, 111.74, 112.77, 113.23, 113.28, 117.36, 119.67, 122.74, 125.17, 127.29, 144.80, 150.56, 157.19, 171.89, 188.12; high resolution mass spectrum for $C_{19}H_{18}O_5$ requires 326.11543, determined 354.10971.

3-Hydroxy-1-[5-(allyloxy)-2-hydroxyphenyl]-3-(3-carbomethoxyphenyl)prop-2-en-1-one (106)

Mp 90-90.5°C; 300 MHz ^1H NMR ($CDCl_3$) δ 3.99 (s, 3 H), 4.51 (dd, 2 H, J = 5.3 Hz, J = 1.2 Hz), 5.23 (dd, 1 H, J = 10.3 Hz, J = 3.6 Hz), 5.41 (dd, 1 H, J = 16.8 Hz, J = 2.7 Hz), 5.71-6.33 (m, 1 H), 6.81 (s, 1 H), 7.01-8.63 (m, 7 H), 12.51 (s, 1 H), 15.60 (s, 1 H); IR ($CDCl_3$) 2970, 1720, 1610, 1570, 1480, 1275, 1195, 1040 cm^{-1}; ^{13}C NMR 52.35, 69.91, 95.52, 113.44, 117.90, 118.45, 119.35, 123.95, 127.65, 128.87, 130.68, 130.81, 132.99, 133.20, 133.78, 150.83, 156.77, 160.04, 176.03, 195.22 ppm; high resolution mass spectrum for $C_{20}H_{18}O_6$ requires 354.11034; determined 354.10971.

3-[4-(2-Propenyl)cyclohexenyl]3-hydroxy-1-
[5-(allyloxy)-2-hydroxyphenyl]prop-2-en-1-one (83)

300 MHz ^{1}H NMR ($CDCl_3$) δ 1.78 (s, 3 H), 2.10-2.31 (m, 2 H), 2.41-2.57 (m, 4 H), 4.52 (d, 2 H, J = 5.5 Hz), 4.77 (d, 2 H, J = 11.6 Hz), 5.31 (d, 1 H, J = 10.2 Hz), 5.43 (d, 1 H, J = 17.1 Hz), 6.01-6.07 (m, 1 H), 6.23 (s, 1 H), 6.91 (d, 1 H, J = 9.1 Hz), 7.04-7.10 (m, 2 H), 7.18 (d, 1 H, J = 3.1 Hz), 11.71 (s, 1 H), 15.08 (s, 1 H); IR (neat) 3200-2850 (br), 2930, 1635, 1565, 1480, 1280, 1180 cm^{-1}; Elemental anal. Calcd for $C_{21}H_{24}O_4$: C, 74.09; H, 7.11. Found: C, 74.07; H, 7.17.

3-Hydroxy-1-[5-allyloxy)-2-hydroxyphenyl]-
3-(5-bromo-2-furyl)prop-2-en-1-one (107)

Mp 72-73°C; 60 MHz ^{1}H NMR ($CDCl_3$) δ 4.56 (d, 2 H, J = 4.1 Hz), 5.16-6.40 (m, 3 H), 6.50 (d, 1 H, J = 3.2 Hz), 7.08-7.46 (m, 5 H), 10.50 (s, 1 H), 14.10 (s, 1 H); IR ($CDCl_3$) 3040, 2980, 1630, 1535, 1480, 1260, 1190, 1095, 1010 cm^{-1}; Elemental anal. Calcd for $C_{16}H_{13}O_5Br$: C, 52.62; H, 3.59. Found: C, 52.71; H, 3.55.

3-Hydroxy-1-[5-(allyloxy)-4-methoxy-2-
hydroxyphenyl]octa-2,4,6-trien-1-one (108)

Mp 110-110.5°C; 300 MHz ^{1}H NMR ($CDCl_3$) δ 1.89 (d, 3 H, J = 5.7 Hz), 3.89 (s, 3 H), 4.54 (d, 2 H, J = 4.8 Hz), 5.30 (d, 1 H, J = 10.8 Hz), 5.40 (d, 1 H, J = 18.0 Hz), 5.88-6.31 (m, 3 H), 5.94 (s, 1 H), 6.44 (s, 1 H), 7.06 (s, 1 H), 7.10-7.31 (m, 1 H), 12.55 (s, 1 H), 14.52 (s, 1 H); IR ($CDCl_3$) 3230-2870 (br), 1613, 1555, 1435, 1250, 1170, 975 cm^{-1}; ^{13}C NMR 18.76, 56.03, 71.40, 95.98, 101.04, 110.68, 113.54, 118.06, 123.43,

130.58, 133.39, 138.49, 139.86, 140.80, 157.11, 160.34, 173.93, 193.93 ppm; high resolution mass spectrum for $C_{18}H_{20}O_5$ requires 316.13108, determined 316.13108.

3-Hydroxy-1-[4-(allyloxy)-1-hydroxy-8-methoxynaphthalenyl]-6-(1,3-dithiolane-2-yl)hepta-2,4-dien-1-one (109)

Mp 134-135°C; 300 MHz ^1H NMR ($CDCl_3$) δ 1.96 (s, 3 H), 3.31-3.52 (m, 4 H), 4.09 (s, 3 H), 5.33 (d, 1 H, J = 11.1 Hz), 5.34 (d, 1 H, J = 12.0 Hz), 6.19 (d, 1 H, J = 15.3 Hz), 6.61 (s, 1 H), 6.95 (d, 1 H, J = 7.1 Hz), 6.99 (d, 1 H, J = 15.3 Hz), 7.17 (s, 1 H), 7.50 (t, 1 H, J = 6.9 Hz), 7.95 (d, 1 H, J = 7.1 Hz), 12.04 (s, 1 H), 15.56 (s, 1 H); IR ($CDCl_3$) 3320, 3150, 2980, 2920, 1630, 1560, 1460, 1400, 1375, 1160, 1060 cm^{-1}; high resolution mass spectrum for $C_{23}H_{24}O_5S_2$ requires 444.10653, determined 444.10674.

3-Hydroxy-1-(2-hydroxyphenyl)hexa-2,4-dien-1-one (110)

Mp 108-110°C; 60 MHz ^1H NMR ($CDCl_3$) δ 1.90 (dd, 3 H, J = 7.4 Hz, J = 1.5 Hz), 5.91 (d, 1 H, J = 17 Hz), 6.21 (s, 1 H), 6.60-7.71 (m, 5 H), 12.21 (s, 1 H), 14.62 (s, 1 H); IR ($CDCl_3$) 3180-2830 (br), 1650, 1570, 1485, 1430, 1300, 1175, 960 cm^{-1}; Elemental anal. Calcd for $C_{12}H_{12}O_3$: C, 70.58; H, 5.92. Found: C, 70.84; H, 5.79.

3-Hydroxy-1-(2-hydroxyphenyl)-5-phenylpenta-2,4-dien-1-one (111)

Mp 132-133°C; 60 MHz ^1H NMR ($CDCl_3$) δ 6.30 (s, 1 H), 6.42-7.80 (m, 11 H), 12.40 (s, 1 H), 15.02 (s, 1 H); IR ($CDCl_3$) 3350-2730 (br), 1630,

1560, 1480, 1430, 1330, 1300, 1170, 980 cm^{-1}; Elemental anal. Calcd for $C_{17}H_{14}O_3$: C, 76.68; H, 5.30. Found: C, 76.48; H, 5.37.

3-Hydroxy-1-(2-hydroxyphenyl)oct-2-en-1-one (112)

60 MHz ^1H NMR ($CDCl_3$) δ 0.62-1.95 (m, 9 H), 2.12-2.72 (m, 2 H), 6.13 (s, 1 H), 6.68-7.78 (m, 4 H), 12.07 (s, 1 H), 15.12 (s, 1 H); IR (neat) 2950, 1640, 1460, 1380, 1300, 1220, 960, 750 cm^{-1}; Elemental anal. Calcd for $C_{14}H_{18}O_3$: C, 71.77; H, 7.74. Found: C, 72.02; H, 8.13.

13-Hydroxy-1-(2-hydroxyphenyl)-3-phenylprop-2-en-1-one (114)

Mp 121-122°C; 60 MHz ^1H NMR ($CDCl_3$) δ 6.3 (s, 1 H), 6.5-7.8 (m, 9 H), 11.6 (s, 1 H), 15.4 (s, 1 H); IR ($CDCl_3$) 3050, 1610, 1565, 1485, 1330, 1295, 1050 cm^{-1}; Elemental anal. Calcd for $C_{15}H_{12}O_3$: C, 74.99; H, 5.03. Found: C, 74.70; H, 4.97.

3-Hydroxy-1-[5-(allyloxy)-4-methoxy-2-hydroxyphenyl]-(5-phenylthio)penta-2,4-dien-1-one (115)

60 MHz ^1H NMR ($CDCl_3$) δ 3.9 (s, 3 H), 4.51 (d, 1 H, J = 5.2 Hz), 5.30-5.42 (m, 2 H), 6.1 (s, 1 H), 6.2-7.2 (m, 3 H), 11.5 (s, 1 H), 14.5 (s, 1 H); IR ($CDCl_3$) 3200-2810 (br), 1610, 1550, 1440, 1255, 1150, 995, 950 cm^{-1}; MS m^+/e 57, 69, 101, 150, 167, 185, 274, 351, 384 (M^+).

3-Hydroxy-1-[5-(allyloxy)-2-hydroxyphenyl]-6-(1,3-dithiolane-2-yl)hepta-2,4-dien-1-one (116)

Mp 94-94.5°C; 300 MHz ^1H NMR ($CDCl_3$) δ 1.97 (s, 3 H), 3.31-3.52 (m, 1 H), 4.51 (d, 2 H, J = 5.2 Hz), 5.31 (dd, 1 H, J = 10.3 Hz, J = 1.5 Hz), 5.42 (dd, 1 H, J = 16.8 Hz, J = 1.5 Hz), 5.95-6.21 (m, 1 H), 6.13 (d, 1

H, J = 16.1 Hz), 6.18 (s, 1 H), 6.81-7.22 (m, 4 H), 11.75 (s, 1 H), 14.61 (s, 1 H); IR ($CDCl_3$) 3200-2850 (br), 1640, 1560, 1485, 1285, 1180, 1045, 960 cm^{-1}; MS m/e 69, 85, 105, 117, 173, 245, 272, 346, 364 (M^+); high resolution mass spectrum for $C_{18}H_{20}O_4S_2$ requires 364.08033, determined 364.08010.

3-Hydroxy-1-[5-(allyloxy)-2-hydroxyphenyl]-6-(1,3-dithian-2-yl)hepta-2,4-dien-1-one (117)

Mp 94-95°C; 300 MHz ^1H NMR ($CDCl_3$) δ 1.67 (s, 3 H), 1.77-2.03 (m, 2 H), 2.70-2.98 (m, 4 H), 4.51 (d, 2 H, J = 5.7 Hz), 5.31 (dd, 1 H, J = 10.2 Hz, J = 1.5 Hz), 5.43 (dd, 1 H, J = 16.7 Hz, J = 1.5 Hz), 5.99-6.13 (m, 1 H), 6.19 (s, 1 H), 6.29 (d, 1 H, J = 15.6 Hz), 6.93 (s, 1 H), 6.94 (d, 1 H, J = 15.6 Hz), 7.02 (s, 1 H), 7.08-7.16 (m, 2 H), 11.74 (s, 1 H), 14.56 (s, 1 H); IR ($CDCl_3$) 3200-2780 (br), 1630, 1555, 1482, 1195, 1045, 955 cm^{-1}; high resolution mass spectrum for $C_{19}H_{22}O_4S_2$ requires 378.09596, determined 378.09578.

Claisen Rearrangement of 132 to 133

To a flame-dried culture tube was added 132 (150 mg, 0.50 mmol) and a small crystal of hydrobenzoquinone as an antioxidant. A 0.1 M solution was made by adding 5 ml of dry benzene and nitrogen was bubbled through the solution for 5 minutes. A teflon-lined cap was screwed on and the solution was heated at 240°C for 18 hours. After cooling and concentration in vacuo, the residue was flash chromatographed using 1:3 hexane: ethyl acetate to afford 122 mg (81%) of 133; 300 MHz ^1H NMR ($CDCl_3$) δ 2.53 (s, 3 H), 3.38 (br d, J = 11.3 Hz), 5.08-5.20 (m, 2 H),

5.58 (s, 1 H), 5.93-6.10 (m, 1 H), 7.07 (s, 1 H), 7.17-7.33 (m, 5 H); IR ($CDCl_3$) 3420, 1685, 1430, 1250, 1175 cm^{-1}; ^{13}C NMR 31.42, 33.17, 116.44, 116.83, 123.75, 126.26, 126.63, 127.99, 128.89, 129.26, 134.69, 135.32, 147.97, 148.14, 204.88 ppm.

General Procedure for the Tandem Claisen-Diels-Alder Reaction

In a dry glass tube was placed the requisite β-diketone and a crystal of hydrobenzoquinone, and diluted with dry benzene (10 ml/mmol). The solution was cooled to -78°C and degassed (three freeze-thaw cycles in vacuo). After sealing a glass tube, the benzene solution was heated at >210°C in a silicon oil bath until the reaction was judged complete by TLC. After cooling to -78°C, the tube was opened, and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography on silica gel using hexane/ethyl acetate as the eluent.

Tricyclic β-diketone 134

Using the general procedure, a solution of β-diketone 86 (260 mg, 1.0 mmol) was heated at 210°C for 12 hours. Isolation gave 218 mg (84%) of pure 134 as a yellow-orange solid; mp 193-195°C; 300 MHz ^1H NMR ($CDCl_3$) δ 1.32 (d, 3 H, J = 10.8 Hz), 1.42-2.83 (m, 7 H), 3.09 (dd, 1 H, J = 15.3 Hz, J = 4.5 Hz), 4.56 (s, 1 H), 6.70 (d, 1 H, J = 9.1 Hz), 7.13 (d, 1 H, J = 9.0 Hz), 11.54 (s, 1 H), 14.53 (s, 1 H); IR ($CDCl_3$) 3590, 3040, 2975, 1605, 1575, 1455, 1415, 1260 cm^{-1}; MS m/e 137, 176, 190, 203, 232, 260 (M^+); high resolution mass spectrum for $C_{15}H_{16}O_4$ requires 260.10486; determined 260.10496.

Tricyclic β-diketone 135

A solution of β-diketone 102 (168 mg, 0.59 mmol) in 6 ml of benzene was heated at 210° C for 12 hours in a sealed tube. Flash chromatography using 1:1 hexane: ethyl acetate gave 117 mg (70%) of 135 as a 10:1 ratio of diastereomeric mixtures. A major isomer was separated by fractional recrystallization from benzene as orange plates. mp 180-181°C; 300 MHz ^{1}H NMR ($CDCl_3$) δ 1.65 (d, 3 H, J = 3.6 Hz), 1.89-1.94 (m, 1 H), 2.24 (br t, 1 H, J = 14.6 Hz), 2.36 and 2.41 (two br s, 1 H), 2.64-2.80 (m, 4 H), 3.07 (dd, 1 H, J = 15.4 Hz, J = 4.6 Hz), 4.53 (s, 1 H), 5.46-5.50 (m, 2 H), 6.69 (d, 1 H, J = 8.9 Hz), 6.92 (d, 1 H, J = 8.9 Hz), 11.54 (s, 1 H), 14.70 (s, 1 H); ^{13}C NMR (D_6-acetone) 16.40, 27.51, 32.13, 33.48, 33.94, 106.34, 114.09, 115.36, 122.78, 123.65, 126.76, 132.00, 144.49, 154.67, 176.94, 192.06 ppm; IR ($CDCl_3$) 3380, 2910, 1610, 1570, 1460, 1310, 1270, 1200 cm^{-1}; high resolution mass spectrum for $C_{17}H_{18}O_4$ requires 286.12051, determined 286.12023; Elemental anal. Calcd for $C_{17}H_{18}O_4$: C, 71.31; H, 6.34. Found: C, 71.17; H, 6.27.

Tricyclic β-diketone 136

A solution of β-diketone 104 (110 mg, 0.40 mmol) in 4 ml of dry benzene was heated at 230°C for 14 hours. Isolation gave 11.1 mg (10%) of 136 as an orange solid: mp 160-162°C; 300 MHz ^{1}H NMR ($CDCl_3$) δ 1.25-3.18 (m, 8 H), 4.91-5.18 (m, 2 H), 5.71-5.89 (m, 1 H), 6.67 (d, 1 H, J = 6.8 Hz), 6.92 (d, 1 H, J = 6.7 Hz), 11.57 (s, 1 H), 14.69 (s, 1 H); IR ($CDCl_3$) 3595, 1606, 1580, 1462, 1260, 1225, 1010 cm^{-1}; high resolution mass spectrum for $C_{16}H_{16}O_4$ requires 272.10429, determined 272.10486.

Tricyclic β-diketone 137

A solution of β-diketone 108 (126 mg, 0.40 mmol) in 4 ml of benzene was heated at 210°C for 10 hours. Evaporation of the solvent afforded pure product 137 as a 4:1 mixture of diastereomers in quantitative yield: mp 182-183°C; 300 MHz ^{1}H NMR ($CDCl_3$) δ 1.64 (d, 3 H, J = 3.9 Hz), 1.86-2.78 (m, 7 H), 3.20 (dd, 1 H, J = 16.3 Hz, J = 3.9 Hz), 3.91 and 3.93 (s, 3 H), 5.23 and 5.21 (s, 1 H), 5.45-5.50 (m, 1 H), 6.33 (s, 1 H), 12.05 and 12.21 (s, 1 H), 14.54 and 15.26 (s, 1 H); IR ($CDCl_3$) 3540, 2940, 1605, 1580, 1440, 1285, 1210 cm^{-1}; high resolution mass spectrum for $C_{18}H_{20}O_5$ requires 316.13018, determined 316.13054.

Tricyclic β-diketone 138

A solution of β-diketone 116 (210 mg, 0.58 mmol) in 6 ml of benzene was heated at 240°C for 18 hours in a sealed tube. The crude product was purified by flash chromatography using a 4:6 hexane:ethyl acetate to afford 178 mg (85%) of compound 138 as a 3.1:1 ratio of diastereomeric mixture. A major diastereomer could be isolated by fractional recrystallization from chloroform as pale yellow plates: mp 187-188°C; 300 MHz ^{1}H NMR ($CDCl_3$) δ 1.82 (s, 3 H), 1.92-2.10 (m, 2 H), 2.3-2.9 (m, 5 H), 3.05 (dd, 1 H, J = 15.3 Hz, J = 4.8 Hz), 4.39 (s, 1 H), 6.66 (d, 1 H, J = 8.7 Hz), 6.92 (d, 1 H, J = 8.7 Hz), 11.57 (s, 1 H), 13.97 (s, 1 H); IR ($CDCl_3$) 3580, 2925, 1620, 1585, 1470, 1220, 975 cm^{-1}; MS m/e 69, 105, 145, 173, 245, 272, 364 (M^+); high resolution mass spectrum for $C_{18}H_{20}O_4S_2$ requires 364.08031, determined 364.08009.

Tricyclic β-diketone 139

A solution of β-diketone 117 (180 mg, 0.476 mmol) in 5 ml of benzene was heated at 240°C for 24 hours. Isolation gave 146 mg (81%) of 139 as a 2.2:1 mixture of diastereomers: mp 190-192°C; 300 MHz ^{1}H NMR ($CDCl_3$) δ 1.61 and 1.63 (s, 3 H), 1.82-3.12 (m, 14 H), 5.23 (br s, 1 H), 6.67-7.13 (m, 2 H), 11.61 and 11.64 (s, 1 H), 13.88 and 14.98 (s, 1 H); IR ($CDCl_3$) 3520, 2935, 1618, 1580, 1470, 1225, 978 cm^{-1}; MS m/e 69, 189, 217, 243, 270, 303, 378 (M^+); high resolution mass spectrum for $C_{19}H_{22}O_4S_2$ requires 378.09596, determined 378.09578.

Tricyclic β-diketone 141

A solution of 100 mg (0.271 mol) of β-diketone 140 in 3 ml of benzene was heated at 230°C for 16 hours. Isolation afforded 68 mg (68%) of product 141 as a single diastereomer: mp 210-211°C; 300 MHz ^{1}H NMR ($CDCl_3$) δ 1.04 (d, 3 H, J = 7.2 Hz), 1.52-2.90 (m, 7 H), 3.08 (dd, 1 H, J = 16.8 Hz, J = 3.8 Hz), 4.38 (s, 1 H), 6.80 (s, 1 H), 7.25-7.41 (m, 5 H), 12.19 (s, 1 H), 14.53 (s, 1 H); IR ($CDCl_3$) 3480, 2965, 1610, 1575, 1460, 1320, 1260, 1205 cm^{-1}; high resolution mass spectrum for $C_{21}H_{20}O_4S$ requires 368.18024, determined 368.10851.

Dethioketalization of 138

To a stirred solution of the thioketal 138 (135 mg, 0.33 mmol) in 4:1 acetonitrile:water (24 ml, 6 ml) were added $HgCl_2$ (186 mg, 0.69 mmol) and yellow HgO (150 mg, 0.70 mmol). The reaction mixture was vigorously stirred for 12 hours at ambient temperature. The suspension was then filtered, washed thoroughly with ethyl acetate, and this solvent was used

for extraction of the product from the concentrated aqueous solution. The organic extracts were dried over magnesium sulfate, filtered, and concentrated in vacuo. The resulting yellow residue was flash chromatographed on silica gel using hexane:ethyl acetate to afford 97 mg (88%) of the tricyclic ketone 143 as a pale yellow solid: mp 201-203°C; 300 MHz ^{1}H NMR ($CDCl_3$) δ 2.08 (s, 3 H), 1.78-3.23 (m, 8 H), 5.02 (s, 1 H), 6.65 (d, 1 H, J = 6.8 Hz), 6.93 (d, 1 H, J = 6.8 Hz), 11.41 (s, 1 H), 14.78 (s, 1 H); IR ($CDCl_3$) 3455, 2978, 1715, 1610, 1430, 1270 cm^{-1}; MS m/e 69, 99, 147, 203, 245, 270, 288 (M^+); high resolution mass spectrum for $C_{16}H_{16}O_5$ requires 288.0998; determined 288.1002.

DDQ Oxidation of 138 to Naphthoquinone 144

To a stirred solution of the tricyclic β-diketone 138 (0.430 g, 1.18 mmol) in 20 ml of dry dioxane at 5°C was added 2.2 equiv. of 2,3-dichloro-4,5-dicyanobenzoquinone (0.590 g, 2.60 mmol). The reaction mixture was stirred at ambient temperature for eight hours. The resulting orange-red suspension was filtered, and the residue was washed thoroughly with the cold methylene chloride. The filtrate and washed were combined and concentrated in vacuo. The residue was flash chromatographed on silica gel using methylene chloride as a solvent to afford 298 mg (70%) of quinone 144 as a yellow-orange solid: mp 174-175°C; 300 MHz ^{1}H NMR ($CDCl_3$) δ 1.94 (s, 3 H), 1.95-2.03 (m, 1 H), 2.6-3.24 (m, 4 H), 3.25-3.47 (m, 4 H), 6.94 (d, 2 H, J = 0.9 Hz), 7.52 (s, 1 H), 13.64 (s, 1 H); IR ($CDCl_3$) 2980, 2915, 1670, 1638, 1595, 1375, 1230, 1100, 1055, 840 cm^{-1}; ^{13}C NMR 30.88, 34.57, 40.30, 40.40, 42.90, 46.20, 69.26, 116.54, 117.67, 121.48, 136.07, 136.76, 140.75, 151.95,

162.92, 184.12, 184.50, 202.25 ppm; high resolution mass spectrum for $C_{18}H_{16}O_4S_2$ requires 362.06460, determined 362.0647.

Conversion of 144 to Anthraquinone 149

Diels-Alder reaction of 144 and 1-trimethylsilyloxybutadiene

To a solution of 230 mg (0.64 mmol) of quinone 144 in 7 ml of dry methylene chloride at 0°C was added 0.34 ml (1.92 mmol) of 1-trimethylsilyloxybutadiene. The reaction was stirred at ambient temperature for 6 hours. The solvent and excess diene was removed *in vacuo*, and the residue was triturated with pentane and filtered to give 310 mg (97%) of practically pure adducts 147 and 148 in a 4:3 ratio: 300 MHz ^1H NMR ($CDCl_3$) δ -0.275 and -0.278 (s, 9 H), 1.84 and 1.88 (s, 3 H), 2.04-2.21 (m, 2 H), 2.48-3.52 (m, 11 H), 4.38-4.46 (m, 1 H), 5.74-5.96 (m, 2 H), 7.38 and 7.45 (s, 1 H), 13.28 and 13.67 (s, 1 H); IR ($CDCl_3$) 2960, 1695, 1640, 1590, 1372, 1250, 1020 cm^{-1}; MS m/e 75, 119, 268, 290, 318, 362, 412 ($M^+\cdot$-$(CH_3)SiOH$) 484; high resolution mass spectrum for $C_{22}H_{20}O_4S_2$ ($M^+\cdot$-$(CH_3)_3SiOH$) requires 412.08031, determined 412.08071.

Aromatization of 147 and 148 to anthraquinone 149

To a stirred solution of 310 mg (0.617 mmol) of the Diels-Alder adduct 147 and 148 in 10 ml of methylene chloride at 0°C was added two equivalents of triethylamine (0.17 ml, 1.24 mmol). The reaction was allowed to warm to ambient temperature over 1 hour. The mixture was diluted with water and acidified with 1N HCl to pH 5. The aqueous phase was extracted with methylene chloride. The combined organic phase was washed with water, dried, and concentrated *in vacuo*. The crude product

was chromatographed on silica gel using 3% ethyl acetate in methylene chloride to afford 177 mg (70%) of anthraquinone 149 as an orange solid: mp 242-244°C; 300 MHz ^{1}H NMR ($CDCl_3$) δ 1.90 (s, 3 H), 1.93-2.83 (m, 3 H), 3.10 (dd, 2 H, J = 16.8 Hz, J = 11.3 Hz), 3.21 (d, 1 H, J = 16.7 Hz), 3.30-3.35 (m, 4 H), 7.70 (s, 1 H), 7.74-8.02 (m, 2 H), 8.24 (d, 1 H, J = 6.9 Hz), 8.31 (d, 1 H, J = 7.5 Hz), 13.95 (s, 1 H); IR ($CDCl_3$) 2980, 1675, 1630, 1592, 1370, 1258, 845 cm^{-1}; MS m/e 59, 119, 290, 317, 333, 348, 408 (M^+); high resolution mass spectrum for $C_{22}H_{18}O_4S_2$ requires 410.0641; determined 410.0640.

$ZnCl_2$-catalyzed Diels-Alder Reaction of 144 and 1-trimethylsilyloxybutadiene

To a stirred solution of naphthoquinone 144 (200 mg, 0.55 mmol) in 10 ml of dry methylene chloride at -23°C was added 75 mg (0.55 mmol) of freshly fused zinc chloride. After stirring at 10 min, 1-trimethylsilyloxybutadiene (0.29 ml, 1.65 mmol) was introduced to the reaction mixture. The reaction was slowly warmed to 0°C over 1 hour and stirred at 0°C for an additional 1 hour. The solution was diluted with 10 ml of methylene chloride and washed with water. The organic phase was dried over magnesium sulfate, filtered, and concentrated *in vacuo* to afford 220 mg (97%) of the crude adducts 147 and 148 in a 50:1 ratio, which were used directly in the next step: 300 MHz ^{1}H NMR ($CDCl_3$) δ -0.278 (s, 3 H), 1.84 (s, 3 H), 2.04-3.20 (m, 8 H), 3.12 (d, 1 H, J = 17.2 Hz), 3.20-3.50 (m, 4 H), 4.37 (t, 1 H, J = 1.3 Hz), 5.76-5.89 (m, 2 H), 7.49 (s, 1 H), 13.66 (s, 1 H). This crude product (100 mg, 0.20 mmol) was treated at 0°C with 2 ml of 1N HCl in THF (10 ml). After stirring at 0°C for 1

hour, the reaction was diluted with ethyl acetate, washed with brine and water, dried over magnesium sulfate. Evaporation of the solvent afforded 81 mg (94%) of the desired allylic alcohol 151 as a pale yellow solid: 300 MHz ^{1}H NMR ($CDCl_3$) δ 1.88 (s, 3 H), 2.13-3.21 (m, 9 H), 3.25-3.49 (m, 4 H), 4.49 (br s, 1 H), 5.71-6.03 (m, 2 H), 7.46 (s, 1 H), 13.6 (br s, 1 H); IR ($CDCl_3$) 3580, 2905, 1630, 1370, 1248, 1045 cm^{-1}.

Tricyclic β-diketone 152

A 251 mg (0.87 mmol) of ketone 143 was dissolved in a mixture of benzene (15 ml), ethylene glycol (100 mg, 1.60 mmol), and several crystals of p-toluensulfonic acid. The reaction was heated at reflux for 3 hours with azeotropic removal of water. The mixture was poured into water, and extracted with ethyl acetate. The organic phase was washed with 10% $NaHCO_3$ solution and saturated brine, dried, and concentrated *in vacuo*. The residue was flash chromatographed on silica gel eluting 4:6 hexane:ethyl acetate to afford 240 mg (83%) of 152 as a yellow solid; 300 MHz ^{1}H NMR ($CDCl_3$) δ 1.25-1.50 (m, 1 H), 1.58 (s, 3 H), 1.66-2.41 (m, 4 H), 2.48 (t, 1 H, J = 5.4 Hz), 2.86-2.96 (m, 1 H), 3.06 (dd, 1 H, J = 15.3 Hz, J = 4.8 Hz), 3.88-4.03 (m, 4 H), 4.53 (s, 1 H), 6.99 (d, 1 H, J = 8.7 Hz), 6.91 (d, 1 H, J = 9.3 Hz), 11.56 (s, 1 H), 14.49 (s, 1 H); IR ($CDCl_3$) 3440, 2975, 1610, 1540, 1430, 1327, 1230, 1105 cm^{-1}; MS m/e 87, 189, 217, 243, 287, 332 (M^+).

Naphthoquinone 153

Using the procedure described for 144, compound 152 (189 mg, 0.57 mmol) was oxidized with 2.2 equivalents of DDQ (284 mg, 1.25 mmol) in 10

ml of dry dioxane. The crude product was purified by flash chromatography using 2% ethyl acetate in methylene chloride to afford 130 mg (69%) of quinone 153 as an orange solid: mp 160-163°C (decomposition); 300 MHz ^{1}H NMR ($CDCl_3$) δ 2.48-2.57 (m, 1 H), 2.70 (dd, 1 H, J = 16.8 Hz, J = 11.7 Hz), 2.89-3.08 (m, 2 H), 3.23 (dd, 1 H, J = 15.6 Hz, J = 2.4 Hz), 3.89-4.08 (m, 4 H), 6.93 (s, 2 H), 7.49 (s, 1 H), 13.66 (s, 1 H); IR ($CDCl_3$) 2990, 1660, 1630 (sh), 1592, 1370, 1210, 1100 cm^{-1}; high resolution mass spectrum for $C_{18}H_{18}O_6$ requires 333.11023, determined 330.10978.

Diels-Alder Adduct 154

Following the same procedure as that used to prepare 147, zinc chloride-catalyzed Diels-Alder reaction of 153 (40 mg, 0.12 mmol) and 1-trimethylsilyloxybutadiene (0.063 ml, 0.36 mmol) was carried out at 0°C in methylene chloride. The crude adduct 154 obtained in 94% yield used directly in the next PCC oxidation step; 300 MHz ^{1}H NMR ($CDCl_3$) δ -0.292 (s, 3 H), 1.33 (s, 3 H), 2.21-3.33 (m, 9 H), 3.89-4.05 (m, 4 H), 4.39 (t, 1 H, J = 1.8 Hz), 5.72-5.93 (m, 2 H), 7.48 (s, 1 H), 13.71 (s, 1 H); IR ($CDCl_3$) 2970, 1690, 1635, 1595, 1370, 1250, 1030 cm^{-1}.

Anthraquinone 155

To a solution of 154 (35 mg, 0.074 mmol) in 5 ml of dry methylene chloride was added PCC (80 mg, 0.37 mmol) followed by 5 µl of glacial acetic acid. The reaction mixture was stirred at room temperature for 4 hours, then filtered through celite. The filtrate was concentrated, and the residue chromatographed on silica gel eluting 5% ethyl acetate in

methylene chloride to afford 8.1 mg (28%) of 155; 300 MHz ^{1}H NMR ($CDCl_3$) δ 1.38 (s, 3 H), 2.31-3.31 (m, 5 H), 3.91-4.03 (m, 4 H), 7.32 (d, 1 H, J = 7.8 Hz), 7.65 (t, 1 H, J = 7.8 Hz), 7.72 (s, 1 H), 7.78 (d, 1 H, J = 7.5 Hz), 12.75 (s, 1 H), 13.96 (s, 1 H); IR ($CDCl_3$) 2920, 1718, 1648, 1590, 1450, 1280, 1205, 955 cm^{-1}.

Conversion of Naphthoquinone 144 to Anthraquinone 162

Diels-Alder reaction of 144 with 1-methoxycyclohexa-1,3-diene

To a solution of 420 mg (1.167 mmol) of 144 in 20 ml of dry dimethyl sulfoxide at room temperature was added 0.28 ml of 1-methoxycyclohexa-1,3-diene (Aldrich technical grade: contains ca. 30% of 1-methoxycyclohexa-1,4-diene). The reaction was stirred at ambient temperature for 12 hours. The solvent and excess diene was removed under reduced pressure and the residue was stirred with 10 M of pentane for 2 hours. The crude adducts 157 and 158 (6.7:1 ratio) were collected by filtration, rinsed with pentane, and used directly the next step with further purification. The crude yield of this reaction was almost quantitative: 300 MHz ^{1}H NMR ($CDCl_3$) δ 1.45-2.10 (m, 6 H), 1.87 (s, 3 H), 2.21-3.52 (m, 10 H), 3.45 and 4.37 (s, 3 H), 5.85-6.10 (m, 2 H), 7.16 and 7.16 (s, 1 H), 13.35 and 13.55 (s, 1 H); IR ($CDCl_3$) 2960, 2922, 1680, 1635, 1600, 1555, 1370, 1220, 1030 cm^{-1}.

Enolization of adduct 157 and 158

To the freshly prepared 1 M solution of sodium methoxide in methanol (7 ml, 7.0 mmol) at 0°C was added slowly over 5 minutes a mixture of the crude Diels-Alder adduct 157 and 158 (550 mg, 1.20 mmol) in the THF (10

ml) and MeOH (10 ml). The solution was stirred at room temperature for 1 hour. The reaction was quenched by adding 1 ml of glacial acetic acid. The reaction mixture was taken up in 30 ml of ethyl acetate, washed with brine, and dried. The solvents were removed in vacuo and the residue chromatographed on silica gel eluting 10:1 methylene chloride: ethyl acetate to afford 421 mg of the desired 40methoxy hydroquinone 159 and its corresponding quinone 160, along with 74 mg of 1-methoxy hydroquinone 161.

4-Methoxy hydroquinone 159: 300 MHz ^{1}H NMR ($CDCl_3$) δ 1.40-1.97 (m, 5 H), 1.88 (s, 3 H), 2.41-3.16 (m, 4 H), 3.22-3.44 (m, 4 H), 3.73 (s, 3 H), 4.27 (d, 1 H, J = 5.5 Hz), 4.68 (s, 1 H), 6.49 (t, 1 H, J = 4.8 Hz), 6.76 (d, 1 H, J = 8.0 Hz), 7.19 (s, 1 H), 10.09 (s, 1 H), 15.49 (s, 1 H).

4-Methoxy hydroquinone 160: 300 MHz ^{1}H NMR ($CDCl_3$) δ 1.40-1.96 (m, 5 H), 1.87 (s, 3 H), 2.51-2.83 (m, 2 H), 2.99 (dd, 1 H, J = 12.8 Hz, J = 4.99 Hz), 3.20 (d, 1 H, J = 16.7 Hz), 3.48-3.70 (m, 4 H), 3.69 (s, 3 H), 4.41 (d, 1 H, J = 3.1 Hz), 6.40 (t, 1 H, J = 6.3 Hz), 6.62 (d, 1 H, J = 7.5 Hz), 7.47 (s, 1 H), 13.69 (s, 1 H); IR ($CDCl_3$) 2920, 1660, 1630, 1595, 1407, 1375, 1250 cm^{-1}.

1-Methoxy hydroquinone 161: 300 MHz ^{1}H NMR ($CDCl_3$) δ 1.50-1.85 (m, 5 H), 1.89 (s, 3 H), 2.09 (dd, 1 H, J = 9.0 Hz, J = 6.3 Hz), 2.48-2.85 (m, 2 H), 2.92 (d, 1 H, J = 13.8 Hz), 3.16 (dd, 1 H, J = 17.7 Hz, J = 4.8 Hz), 4.35 (d, 1 H, J = 5.4 Hz), 6.58 (t, 1 H, J = 6.3 Hz), 6.67 (d, 1 H, J = 7.5 Hz), 7.39 (s, 1 H), 9.17 (s, 1 H), 9.25 (s, 1 H), 15.70 (s, 1 H).

Oxidative aromatization of 159 and 160 to 162

A mixture of hydroquinone 159 and 160 (208 mg, approx. 0.44 mmol) was heated at reflux in xylene (10 ml) with silver (I) oxide (616 mg, 2.66 mmol) for 30 minutes. The hot solution was filtered to remove the silver salt, and the crude product was precipitated by adding pentane. Filtration chromatography using 5:1 methylene chloride: ethyl acetate afforded 184 mg (95%) of the desired anthraquinone 162 as a yellow-orange solid. The overall yield from quinone 144 was 73%: 300 MHz ^{1}H NMR ($CDCl_3$) δ 1.89 (s, 3 H), 2.58 (dd, 1 H, J = 10.7 Hz, J = 2.7 Hz), 2.72 (apparent t, J = 13.5 Hz), 3.04 (dd, 1 H, J = 16.2 Hz, J = 11.7 Hz), 3.17 (dd, 1 H, J = 16.2 Hz, J = 2.4 Hz), 3.28-3.51 (m, 5 H), 4.06 (s, 3 H), 7.37 (d, 1 H, J = 7.2 Hz), 7.60 (s, 1 H), 7.72 (t, 1 H, J = 7.8 Hz), 7.88 (d, 1 H, J = 7.5 Hz), 14.14 (s, 1 H); IR ($CDCl_3$) 2960, 1670, 1585, 1330, 1260, 1010 cm^{-1}; high resolution mass spectrum for $C_{23}H_{22}O_5S_2$ requires 442.09088, determined 442.09015. Following the same procedure described above, the minor product 1-methoxy hydroquinone 161 (47 mg, 0.10 mmol) was converted to anthraquinone 163 with silver (I) oxide (130 mg, 0.56 mmol) in refluxing xylene in 94% yield: 300 MHz ^{1}H NMR ($CDCl_3$) δ 1.89 (s, 3 H), 2.60 (dd, 1 H, J = 9.0 Hz, J = 2.7 Hz), 2.75 (dd, J = 16.2 Hz, J = 13.5 Hz), 3.05 (dd, J = 16.5 Hz, J = 12.0 Hz), 3.19 (dd, 1 H, J = 16.5 Hz, J = 12.4 Hz), 3.30-3.52 (m, 5 H), 4.05 (s, 3 H), 7.33 (d, 1 H, J = 7.7 Hz), 7.63 (s, 1 H), 7.48 (t, 1 H, J = 7.1 Hz), 7.96 (d, 1 H, J = 7.8 Hz), 13.87 (s, 1 H); IR ($CDCl_3$) 2956, 1660, 1580, 1321, 1270, 1250, 1010 cm^{-1}; MS m/e 119, 322, 379, 442 (M^+).

O-Demethylation of Anthraquinone 162

The anthraquinone 162 (10 mg, 0.023 mmol) in methylen chloride (3 ml) was treated dropwise at 0°C with BBr_3 (0.46 ml of a 1 M solution in hexane). After stirring at 0°C for 1 hour, the resulting red solution was diluted with 5 ml of water and stirred at room temperature for 10 minutes. The organic layer was separated, and the aqueous layer was extracted with methylene chloride. The combined organic extracts were washed with water, dried, and concentrated. The crude product was purified by preparative TLC to provide 8.3 mg (86%) of 164: 300 MHz ^1H NMR ($CDCl_3$) δ 1.89 (s, 3 H), 2.12-3.14 (m, 4 H), 3.23-3.51 (m, 5 H), 7.31 (d, 1 H, J = 7.2 Hz), 7.65 (t, 1 H, J = 6.9 Hz), 7.75 (s, 1 H), 7.79 (d, 1 H, J = 7.1 Hz), 12.69 (s, 1 H), 13.59 (s, 1 H); IR ($CDCl_3$) 2920, 1670 (sh), 1648, 1592, 1450, 1372, 1208, 840 cm^{-1}; MS m/e 119, 176, 205, 308, 331, 426 (M^+).

O-Demethylation of Anthraquinone 163

According to the procedure described in the o-demethylation of 162, the reaction of 163 (5 mg, 11.5 µmol) with BBr_3 (0.23 ml of a 1 M solution in hexane) was carried out at 0°C for 1 hour in methylene chloride. Aqueous work-up followed by isolation gave 4.1 mg (83%) of 165: 300 MHz ^1H NMR ($CDCl_3$) δ 1.83 (s, 3 H), 2.12-3.14 (m, 4 H), 3.23-3.49 (m, 5 H), 7.23 (d, 1 H, J = 7.1 Hz), 7.63 (t, 1 H, J = 7.0 Hz), 7.69 (s, 1 H), 7.79 (d, 1 H, J = 7.1 Hz), 12.31 (s, 1 H), 13.92 (s, 1 H); IR ($CDCl_3$) 2923, 1685 (sh) 1670, 1630, 1598, 1455, 1372, 1252 cm^{-1}.

Sodium Cyanoborohydride Reduction of Ketoquinone 149

To a stirred solution of 110 mg (0.268 mmol) of the ketoquinone 149 in methylene chloride (10 ml) and methanol (10 ml) at room temperature was added glacial acetic acid (1.15 ml) to give a solution of pH 5. A 120 mg (7 equiv) of sodium cyanoborohydride was added and the solution stirred at ambient temperature for 3 hours. The reaction mixture was then diluted with methylene chloride, washed with water, dried, and concentrated. The resulting orange residue was chromatographed on silica gel eluting 3% ethyl acetate in methylene chloride to afford 96 mg (87%) of 166a as a light yellow solid: 300 MHz ^{1}H NMR ($CDCl_3$) δ 1.88 (s, 3 H), 1.70-1.92 (m, 2 H), 2.10-2.22 (m, 1 H), 2.47-3.47 (m, 6 H), 4.30 (s, 1 H), 5.14-5.26 (t, 1 H, J = 6.7 Hz), 7.60 (s, 1 H), 7.75-7.90 (m, 2 H), 8.20-8.40 (m, 2 H), 13.50 (s, 1 H); IR ($CDCl_3$) 3560, 2935, 1670, 1630, 1590, 1430, 1385, 1350, 1270, 970 cm^{-1}; MS m/e 119, 189, 275, 301, 317, 394, 412; high resolution mass spectrum for $C_{22}H_{20}O_4S_2$ requires 412.08031, determined 412.08071.

Sodium Cyanoborohydride Reduction of Ketoquinone 162

Using the same procedure described above for 166a, the ketoquinone 162 (63.5 mg, 0.144 mmol) was reduced to the hydroxyquinone 166b with sodium cyanoborohydride (90 mg, 1.43 mmol) in methylene chloride (8 ml) and methanol (8 ml). Isolation gave 40 mg (63%) of 166b as an orange solid: 300 MHz ^{1}H NMR ($CDCl_3$) δ 1.84 (s, 3 H), 1.80-1.95 (m, 1 H), 2.08-2.87 (m, 2 H), 2.81 (dd, 1 H, J = 16.5 Hz, J = 12.0 Hz), 3.18 (d, 1 H, J = 16.8 Hz), 3.27-3.44 (m, 4 H), 4.06 (s, 3 H), 4.38 (s, 1 H), 5.21 (m, 1 H), 7.45 (d, 1 H, J = 7.2 Hz), 7.73 (t, 1 H, J = 8.1 Hz), 7.93 (d,

1 H, J = 7.5 Hz), 13.92 (s, 1 H); MS (m/e) 119, 292, 380, 393, 412, 426 (M^+-H_2O).

Dethioketalization of 166a

To a stirred solution of the thioketal 166a (135 mg, 0.33 mmol) in acetonile (24 ml) and water (6 ml) was added $HgCl_2$ (186 mg, 10.69 mmol) followed by yellow HgO (150 mg, 10.70 mmol). The reaction mixture was vigorously stirred at room temperature for 16 hours. The solution was then filtered, rinsed thoroughly with ethyl acetate, and this solvent was used for extraction of the product from the concentrated aqueous solution. The organic phase was dried over magnesium sulfate, filtered, and concentrated in vacuo. The residue was chromatographed on silica gel eluting 1:1 hexane:ethyl acetate to afford 97 mg (90%) of pure 167a as a yellow-orange solid: mp 175-177°C; 300 MHz ^1H NMR ($CDCl_3$) δ 2.13-2.26 (m, 2 H), 2.31 (s, 3 H), 2.41-2.53 (m, 1 H), 2.81-2.99 (m, 2 H), 3.21 (dd, 1 H, J = 16.3 Hz, J = 3.3 Hz), 3.72 (br s, 1 H), 5.23 (m, 1 H), 7.64 (s, 1 H), 7.75-7.83 (m, 2 H), 8.30-8.34 (m, 2 H), 13.89 (s, 1 H); IR ($CDCl_3$) 3550, 2925, 1710, 1670, 1630, 1595, 1470, 1350, 1270 cm^{-1}: MS m/e 83, 152, 238, 275, 318, 336 (M^+); high resolution mass spectrum for $C_{20}H_{16}O_5$ requires 336.09978, determined 336.10005.

Dethioketalization of 166b

Using the same procedure described above for compound 167a, the thioketal group of 166b (38 mg, 0.086 mmol) was removed with two equivalents of $HgCl_2$ and HgO in aqueous acetonitrile. The crude product was chromatographed on silica gel using 3:7 hexane: ethyl acetate to

afford 27.7 mg (88%) of pure 167b as an orange solid: mp 183-184°C; 300 MHz ^{1}H NMR ($CDCl_3$) δ 2.13-2.28 (m, 1 H), 2.30 (s, 3 H), 2.43-2.55 (m, 1 H), 3.19 (dd, 1 H, J = 16.8 Hz, J = 8.1 Hz), 3.82 (s, 1 H), 4.08 (s, 3 H), 5.24 (m, 1 H), 7.37 (d, 1 H, J = 8.1 Hz), 7.61 (s, 1 H), 7.76 (t, 1 H, J = 8.1 Hz), 7.97 (d, 1 H, J = 6.9 Hz), 13.84 (s, 1 H); MS 268, 290, 305, 328, 346, 366 (M^+); high resolution mass spectrum for $C_{21}H_{18}O_6$ requires 366.11034, determined 366.11002.

Formation of Acetonide 168a

To a stirred solution of hydroxy ketone 167a (30 mg, 0.089 mmol) in 7 ml of methylene chloride at 0°C was added 2-methoxypropene (0.14 ml, 1.43 mmol) followed by a small crystal of p-toluenesulfonic acid in 2 ml of methylene chloride. The reaction was stirred at room temperature for 3 hours. The reaction mixture was diluted with 10 ml of methylene chloride and washed with 10% sodium bicarbonate solution and brine. The organic phase was dried, concentrated *in vacuo* and the residue chromatographed on silica gel eluting 3:2 hexane: ethyl acetate to yield 26 mg (77%) of the desired acetonide 168a as a mixture of diastereomers: Higher Rf diastereomer (major), mp 159-161°C; 300 MHz ^{1}H NMR ($CDCl_3$) δ 1.59 (s, 3 H), 1.63 (s, 3 H), 2.21 (s, 3 H), 2.38-2.47 (m, 2 H), 2.92-3.14 (m, 3 H), 4.83 (dd, 1 H, J = 10.8 Hz, J = 5.1 Hz), 7.70 (s, 1 H), 7.36-7.57 (m, 3 H), 8.27 (d, 1 H, J = 5.7 Hz); IR ($CDCl_3$) 3005, 2940, 1715, 1660, 1605, 1590, 1460, 1330, 1270, 1210, 1070 cm^{-1}; high resolution mass spectrum for $C_{23}H_{20}O_5$ requires 376.13108, determined 376.13070. Lower Rf diastereomer (minor): 300 MHz ^{1}H NMR ($CDCl_3$) δ 1.72 (s, 3 H), 1.74 (s, 3 H), 2.30 (s, 3 H), 2.48-2.57 (m, 2 H), 2.94-3.20 (m, 3 H), 4.97 (dd, J =

12.1 Hz, J = 6.3 Hz), 7.72 (s, 1 H), 7.71-7.83 (m, 2 H), 8.13-8.29 (m, 2 H); IR ($CDCl_3$) 2995, 2920, 1715, 1670, 1589, 1450, 1345, 1273, 1142 cm^{-1}; MS m/e 189, 217, 247, 275, 301, 306, 376 (M^+).

Formation of Acetonide 168b

The hydroxy ketone 167b (14.1 mg, 0.038 mmol) was converted to the acetonide 168b using the same procedure as that employed for 168a. Isolation afforded 12.2 mg (78%) of 168b: 300 MHz ^1H NMR ($CDCl_3$) δ 1.69 (s, 3 H), 1.71 (s, 3 H), 2.28 (s, 3 H), 2.22-2.34 (m, 1 H), 2.46-2.57 (m, 1 H), 2.92-3.13 (m, 3 H), 4.02 (s, 3 H), 4.94 (dd, 1 H, J = 11.4 Hz, J = 5.1 Hz), 7.31 (d, 1 H, J = 8.1 Hz), 7.62 (s, 1 H), 7.63 (t, 1 H, J = 7.8 Hz), 7.85 (d, 1 H, J = 7.5 Hz).

Formation of Hydroxyketone 169a

The acetonide 168a (40 mg, 0.107 mmol) and trimethyl phosphite (70 mg, 0.37 mmol) were dissolved in 10 ml of dry tert-butanol and 6 ml of THF and cooled to -23°C under N_2. Oxygen was then bubbled through for 5 min and a mixture of tert-butoxide/ter-butanol complex in 3 ml of tert-butanol and 2 ml of THF at -23°C was added quickly and oxygen bubbled through again for 15 minutes. The reaction was quenched by adding 3 ml of water and then carbon dioxide was bubbled through the solution until the solution was neutral. The solvents were removed in vacuo and the residue was extracted with ethyl acetate, dried, and concentrated in vacuo. The crude product was chromatographed on silica gel eluting 4:6 hexane: ethyl acetate to afford 32 mg (77%) of pure 169a as a mixture of diastereomers: 300 MHz ^1H NMR ($CDCl_3$) δ 1.62 and 1.64

(s, 3 H), 1.74 and 1.76 (s, 3 H), 1.78-3.34 (m, 4 H), 2.27 and 2.45 (s, 3 H), 3.60 and 4.30 (s, OH, 1 H), 4.89 and 5.26 (two dd, 1 H, J = 10.5 Hz, J = 6.9 Hz and J = 11.4 Hz and 4.8 Hz), 7.76-7.82 (m, 3 H), 8.28-8.33 (m, 2 H); IR ($CDCl_3$) 3480, 1710, 1670, 1630, 1345, 1275, 1045 cm^{-1}; MS m/e 189, 217, 245, 273, 291, 301, 316, 358, 374, 392 (M^+); high resolution mass spectrum for $C_{23}H_{20}O_6$ (M^+-H_2O) requires 374.11542, determined 374.11560.

Formation of Hydroxyketone 169b

The acetonide 168b (8.0 mg, 0.020 mmol) was converted to the hydroxy ketone 169b using the same procedure as that employed for 169a. Isolation gave 6.6 mg (80%) of 169b as a mixture of diastereomers: 300 MHz ^1H NMR ($CDCl_3$) δ 1.58 and 1.62 (s, 3 H), 1.70 and 1.74 (s, 3 H), 1.83-3.31 (m, 4 H), 2.24 and 2.43 (s, 3 H), 4.03 (s, 3 H), 4. and 4.01 (s, OH, 1 H), 4.87 and 5.22 (two dd, 1 H, J = 10.2 Hz, J = 7.2 Hz and J = 10.7 Hz, J = 5.1 Hz), 7.30-7.88 (m, 4 H).

4-Demethoxy-11-deoxydaunomycinone 146 and its 7-epimer 170

To a stirred solution of the acetonide 169a (29 mg, 0.073 mmol) in 5 ml of wet methylene chloride was added at 0°C a small crystal of p-toluenesulfonic acid in 2 ml of methylene chloride. The reaction was allowed to warm to room temperature over 30 minutes and stirring continued for 3 hours. The reaction mixture was diluted with methylene chloride, washed with 10% sodium bicarbonate solution and water. Drying of the organic layer over magnesium sulfate, followed this mixture was chromatographed on silica gel eluting 4:6 hexane: ethyl acetate to

afford 14.5 mg of 146 and 7.5 mg of 170 (combined yield, 86%). (+) 4-Dethoxy-11-deoxydaunomycinone 146: mp 201-204°C (dec) [lit mp 199-207°C (dec)] 300 MHz ^{1}H NMR ($CDCl_3$) δ 2.22 (d, 1 H, J = 4.8 Hz), 2.33-2.38 (m, 1 H), 2.42 (s, 3 H), 3.01 (dd, 1 H, J = 17.7 Hz, J = 2.4 Hz), 3.28 (d, 1 H, J = 17.0 Hz), 3.33 (d, 1 H, J = 4.8 Hz), 4.58 (s, 1 H), 5.36 (m, 1 H), 7.64 (s, 1 H), 7.81-7.84 (m, 2 H), 8.28-8.33 (m, 2 H), 13.26 (s, 1 H); IR ($CDCl_3$) 3480, 1710, 1670, 1630, 1595, 1475, 1425, 1380, 1270, 980 cm-1; MS m/e 189, 217, 263, 273, 291, 301, 316, 352 (M^+); high resolution mass spectrum for $C_{20}H_{16}O_6$ requires 352.09469, determined 352.09440. (+) 4-demethoxy-11-deoxy-7-epidaunominone 170: 300 MHz ^{1}H NMR ($CDCl_3$) δ 2.25 (d, 1 H, J = 5.7 Hz), 2.40 (s, 3 H), 2.48 (dd, 1 H, J = 6.9 Hz, J = 2.7 Hz), 2.78 (dd, 1 H, J = 16.8 Hz, J = 2.1 Hz), 3.41 (d, 1 H, J = 16.8 Hz), 3.83 (s, 1 H), 4.14 (d, 1 H, J = 1.8 Hz), 5.43 (m, 1 H), 7.63 (s, 1 H), 7.75-7.80 (m, 2 H), 8.25-8.30 (m, 2 H), 13.53 (s, 1 H).

11-Deoxy-7-epidaunomyconine 171

Using the same procedure described above, the acetonide 169b (6.6 mg, 15.6 μmol) was hydrolyzed in wet methylene chloride containing a catalytic amount of p-toluene sulfonic acid. The crude product was purified by preparative TLC (6:4 hexane:ethyl acetate) to afford 5.1 mg (85%) of 11-deoxy-7-epidaunomycinone 171 as an orange-yellow solid. mp 210-212°C; 300 MHz ^{1}H NMR ($CDCl_3$) δ 2.15-2.50 (m, 2 H), 2.39 (s, 3 H), 2.76 (dd, 1 H, J = 16.8 Hz, J = 2.1 Hz), 3.38 (d, 1 H, J = 16.8 Hz), 4.09 (s, 3 H), 4.25 (s, 1 H), 5.41 (m, 1 H), 7.38 (d, 1 H, J = 8.4 Hz), 7.56 (s, 1 H), 7.77 (t, 1 H, J = 8.1 Hz), 7.96 (d, 1 H, J = 8.5 Hz), 13.94 (s, 1 H); IR

($CDCl_3$) 3460, 2985, 1710, 1670, 1630, 1590, 1210 cm^{-1}; MS m/e 176, 293, 321, 346, 382 (M^+); high resolution mass spectrum for $C_{21}H_{18}O_7$ requires 382.10526, determined 382.10513. As further proof of the structure the 7-hydroxyl group of 171 was removed by catalytic hydrogenation (H_2, 5% $Pd/BaSO_4$, ethyl acetate) to produce 7,11-dideoxydaunomycinone 5. This compound is identical with that described in the literature according to NMR and IR spectra: 300 MHz ^1H NMR ($CDCl_3$) δ 1.87-2.13 (m, 2 H), 2.36 (s, 1 H), 2.79 (d, 1 H, J = 16.5 Hz), 2.90-3.13 (m, 2 H), 3.31 (d, 1 H, J = 16.8 Hz), 3.70 (s, 1 H), 4.09 (s, 3 H), 7.36 (d, 1 H, J = 8.4 Hz), 7.56 (s, 1 H), 7.74 (t, 1 H, J = 7.8 Hz), 7.96 (d, 1 H, J = 7.5 Hz), 13.43 (s, 1 H); IR ($CDCl_3$) 2925, 1715, 1670 (sh), 1625, 1585, 1370 cm^{-1}; high resolution mass spectrum for $C_{21}H_{18}O_6$ requires 366.11034, determined 366.10978.

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PART II. DIELS-ALDER REACTIONS OF QUINONE SULFOXIDES

HISTORICAL

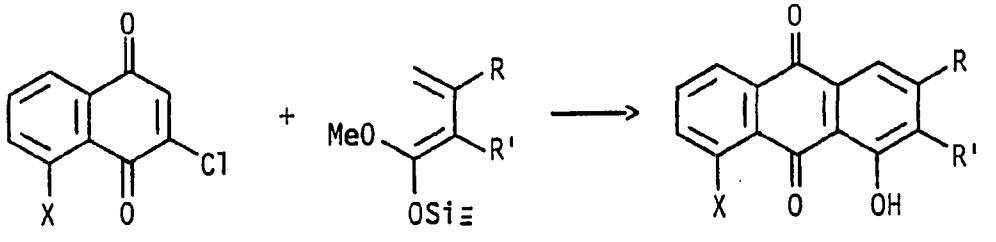
Diels-Alder reactions involving the addition of dienes to either benzoquinones or naphthoquinones have played an important role in elegant syntheses of many natural products. Diels-Alder cycloadditions to p-benzoquinones have been the cornerstone of syntheses of steroids,[1] cortisone,[2] reserpine, yohimbine, estrone, and terramycin,[3] among others. Corey's stereospecific total synthesis of gibberellic acid is a recent demonstration of the utility of a regioselective Diels-Alder reaction involving a substituted benzoquinone.[4]

Recent interest in quinone cycloadditions has intensified due to the feverish activity directed towards the synthesis of anthracycline antibiotics. Synthetic approaches to these and related compounds have featured Diels-Alder cycloaddition to naphthoquinones or anthraquinones.[5] As a fringe benefit, much information has been accumulated about the regioselectivity of these cycloadditions. While the ability to control the regiochemical outcome of such cycloadditions has been a major synthetic challenge, it is only recently that the large number of experimental results have been rationalized in terms of Frontier Molecular Orbital Theory.[6]

In general, Diels-Alder reactions between unsymmetrical quinones, such as juglone derivatives, and dienes produce a mixture of regioisomers.[7] However, this unfavorable result can be overcome in some cases by applying Lewis acid,[7b,8] specific (highly polarized) dienes[9] and dienophiles[10] or substrates with functional groups having complementary effects.[11] These conditions restrict the usefulness of the process. For

example, many dienes do not survive reaction conditions involving classical Lewis acids such as $BF_3 \cdot Et_2O$ or $AlCl_3$ and any gain in regioselectivity is sometimes offset by a decrease in adduct yield. Moreover, attempts to reverse the regiochemical outcome through catalysis,[8a,12] or functional group modifications[11] usually are either unpredictable or give mixtures of regioisomers.

As a possible solution to some of these problems, several researchers, most notably Gesson and Brassard, have determined that the presence of a chlorine or bromine atom on the starting quinone permits the ready assemblage of polycyclic quinones with high regiochemical control.[13] The halogen atom directs the regioselectivity and also



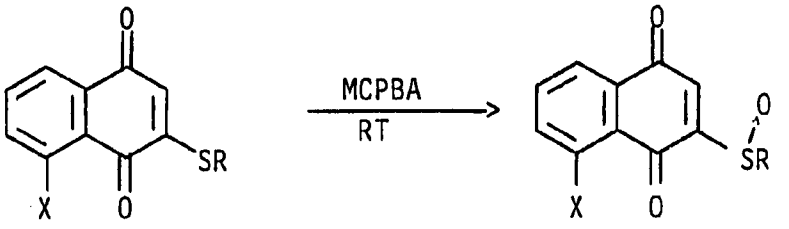
X = H, OH, OCH_3

facilitates the aromatization with the elimination of HBr or HCl. Recently, Bauman and coworkers have reported improved yields of certain anthraquinones by the simple expedient of delaying the dehydrohalogenation step.[14] This haloquinone strategy has been successfully applied to the synthesis of several 11-deoxyanthracyclines.[5]

RESULTS AND DISCUSSION

As part of our synthetic program leading to anthracycline antibiotics, we were interested in developing an efficient method for the synthesis of polycyclic quinones. Although the haloquinone strategy described above is useful for annulating quinones, there are some limitations. For example, the requisite haloquinones may not be easily synthesized, especially if the halogen group must be introduced late in the synthetic sequence. This is particularly difficult if an alkene or amine is present. As convenient alternatives to haloquinones, we considered the sulfinyl quinones. The advantage of this choice was that with appropriate selection of reaction conditions, sulfoxide elimination can regenerate the quinone unit in situ during the Diels-Alder reaction. Furthermore, with quinones such as juglone, either 2- or 3-sulfinyl quinones can be prepared.[15]

Despite the well-known electron-withdrawing effect of the sulfoxide group and the use of vinyl sulfoxides as dienophiles, the use of sulfinyl quinones in the Diels-Alder reaction has only once been reported.[7b] The starting sulfinyl quinones 3 and 4 used for this study could be prepared readily by oxidation of the corresponding known sulfides with MCPBA in methylene chloride[16] as shown below.

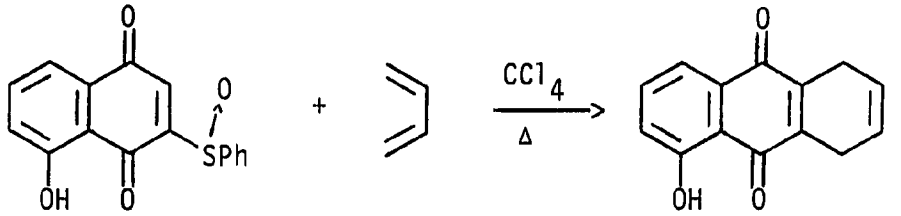


1: X = H R = CH_3 3

2: X = OH R = Ph 4

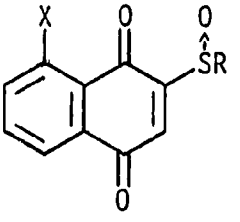
The results of a study of Diels-Alder reactions of quinone sulfoxides 3 and 4 with various dienes are listed in Table 1. These reactions are operationally convenient and have been conducted on scales ranging from 0.5 to 40 mmole. The mild conditions required to effect both the Diels-Alder reaction and the sulfoxide elimination represent a useful feature of this reaction. As expected, when the Diels-Alder cycloaddition was carried out with dienes containing an eliminatable group at C-1, only anthraquinone products were obtained. The aromatization to form an anthraquinone is well precedented.

The utility of quinone sulfoxide Diels-Alder reactions is illustrated further by the preparation of dihydroanthraquinones (Entries 3 and 8). As shown below, the sulfoxide is eliminated regiospecifically to form 1,4-tetrahydro-5-hydroxyanthraquinone 8. This aspect was expected in light of rate studies on sulfoxide eliminations.[17]

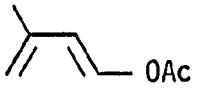
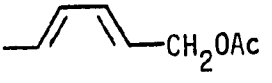
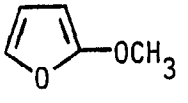


4 8

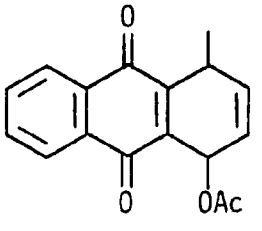
Table 1. Quinone sulfoxide Diels-Alder reactions



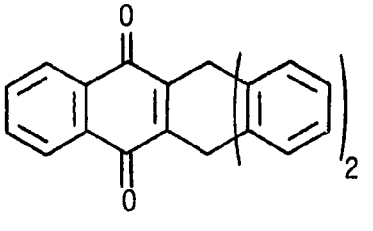
+ DIENE ⟶ ADDUCT[a]

Entry	X	R	diene	% yield	adduct
1	H	CH_3		74	anthraquinone
2	H	CH_3		85	2-methyl anthraquinone
3	H	CH_3		74	5
4	H	CH_3	anthracene	6	6
5	H	CH_3		65	7

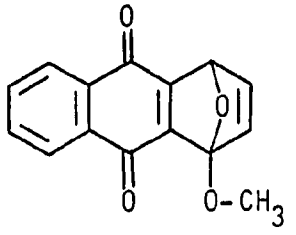
a



5

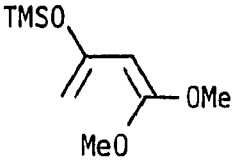


6

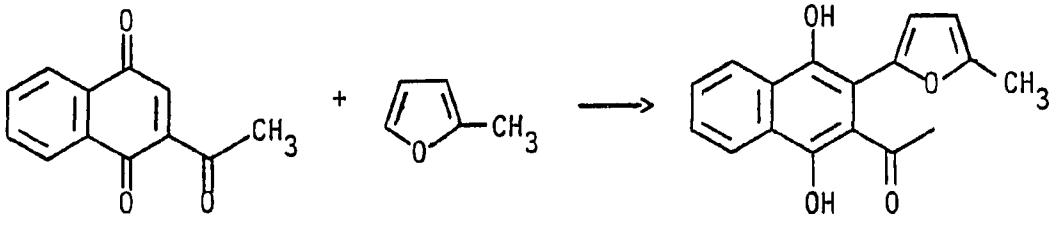


7

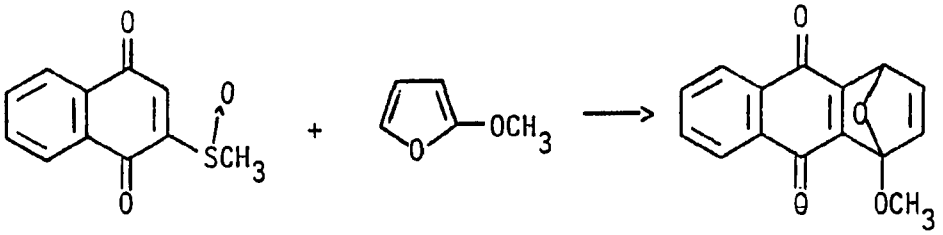
Table 1. Continued

Entry	X	R	diene	% yield	adduct
6	H	CH_3		90	1-methoxy-3-hydroxy anthraquinone
7	OH	Ph		75	1-hydroxy anthraquinone
8	OH	Ph		80	1,4-tetrahydro-5-hydroxy anthraquinone 8

The reaction denoted in Entry 5 is noteworthy in that furans often afford abnormal results in Diels-Alder reactions with quinone-bearing electron-withdrawing group.[18] For example, reaction of furan 10 with 2-acetylnaphthoquinone 9 yields the 1,4-addition product 11. However, in our case, sulfoxide elimination makes the process irreversible to afford Diels-Alder adduct 7.

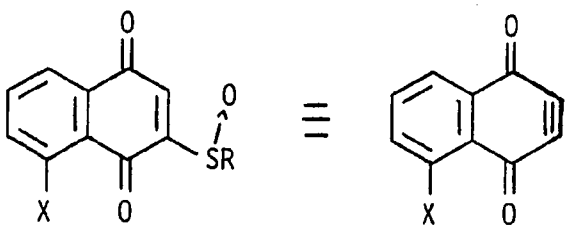


9 10 11



3 7

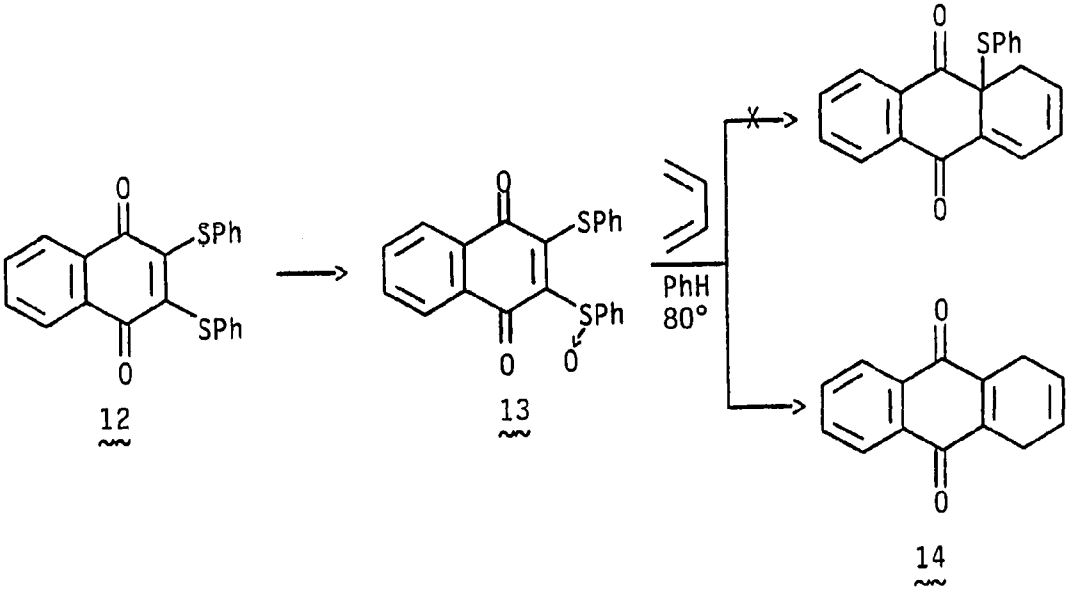
The quinone sulfoxide represents a synthetic equivalent of the unknown compound naphthyquinone.



X = H, OH

While selenoxides undergo elimination much faster than sulfoxides, the analogous phenylselenyl quinones proved difficult to prepare. Oxidation to afford the selenoxide produced several products.

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, 2,3-disulfinylnaphthoquinone 12 was prepared following a literature procedure.[19] Subsequent oxidation of 12 with MCPBA afforded the sulfoxide 13 as a yellow crystalline solid in 78% yield. Interestingly, with naphthoquinone 13, which was designed to prevent reformation of the quinone subunit by elimination of phenylsulfinic acid, the apparent expulsion of PhSOSPh is observed!



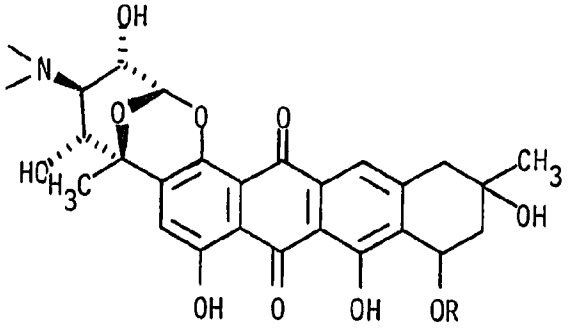
The product 14, which was formed in 63% yield, was readily identified by mass spectroscopy combined with carbon and proton NMR spectroscopy.

To the best of our knowledge, this novel reaction has not previously been observed.

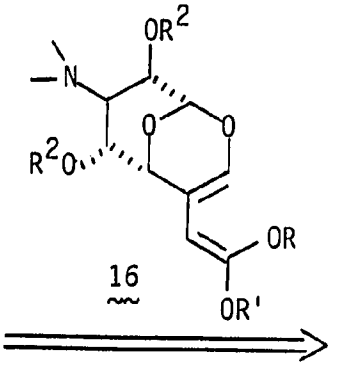
Encouraged by the successful results described above, we decided to explore this method for the synthesis of the tetracyclic system of anthracyclinones. Of particular interest to us was the possibility that the Diels-Alder reaction of the tricyclic quinone sulfoxide 17 with a sugar diene such as 16 might be employed to quickly assemble the tetracyclic framework of nogalamycin (15) with full regiochemical control. The basic concept is outlined in Scheme 1.

While the preparation of the A-ring precursor containing the sugar moiety was undertaken by other coworkers in these laboratories, efficient routes to 17 were sought. Our initial approaches to quinone sulfoxide 17 utilized the tricyclic β-diketone 18a which has been previously prepared (see Table 2, Part 1). Treatment of 18a with two equivalents of DDQ in benzene at room temperature provided quinone 20 in 68% yield. Analogous to findings by Thompson,[15] it was anticipated that the benzenethiol addition to quinone 20 might occur with high control of regioselectivity. Indeed, treatment of 20 with benzenethiol followed by *in situ* oxidation of the resultant hydroquinone with $K_2Cr_2O_7$ in ethanol produced only one detectable product by TLC analysis. The formation of a single regioisomer was further evidenced by the 300 MHz proton NMR spectrum of the crude reaction product which displays two sharp singlets at 6.93 and 13.73 ppm for the corresponding vinylic and chelated hydroxy proton, respectively. However, we were not able to determine by NMR if the product obtained was the desired quinone 21 or its regioisomer.

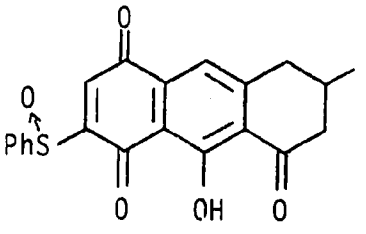
Scheme 1



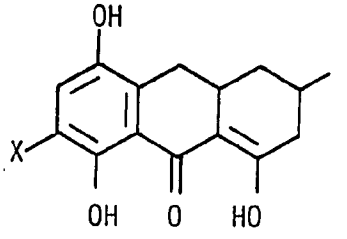
15



16

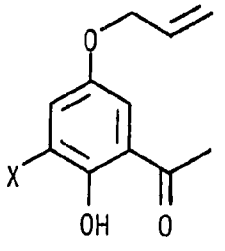


17



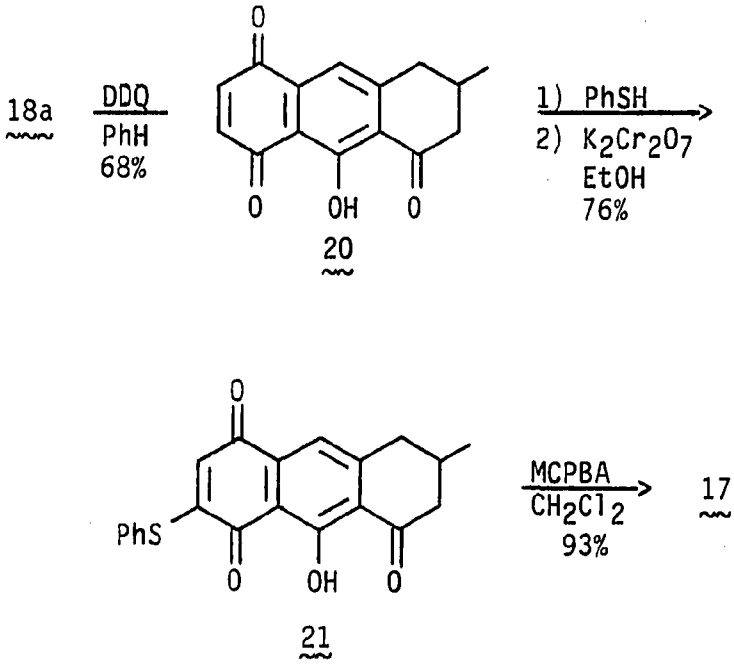
18 a: X = H

b: X = SPh



19 a: X = H

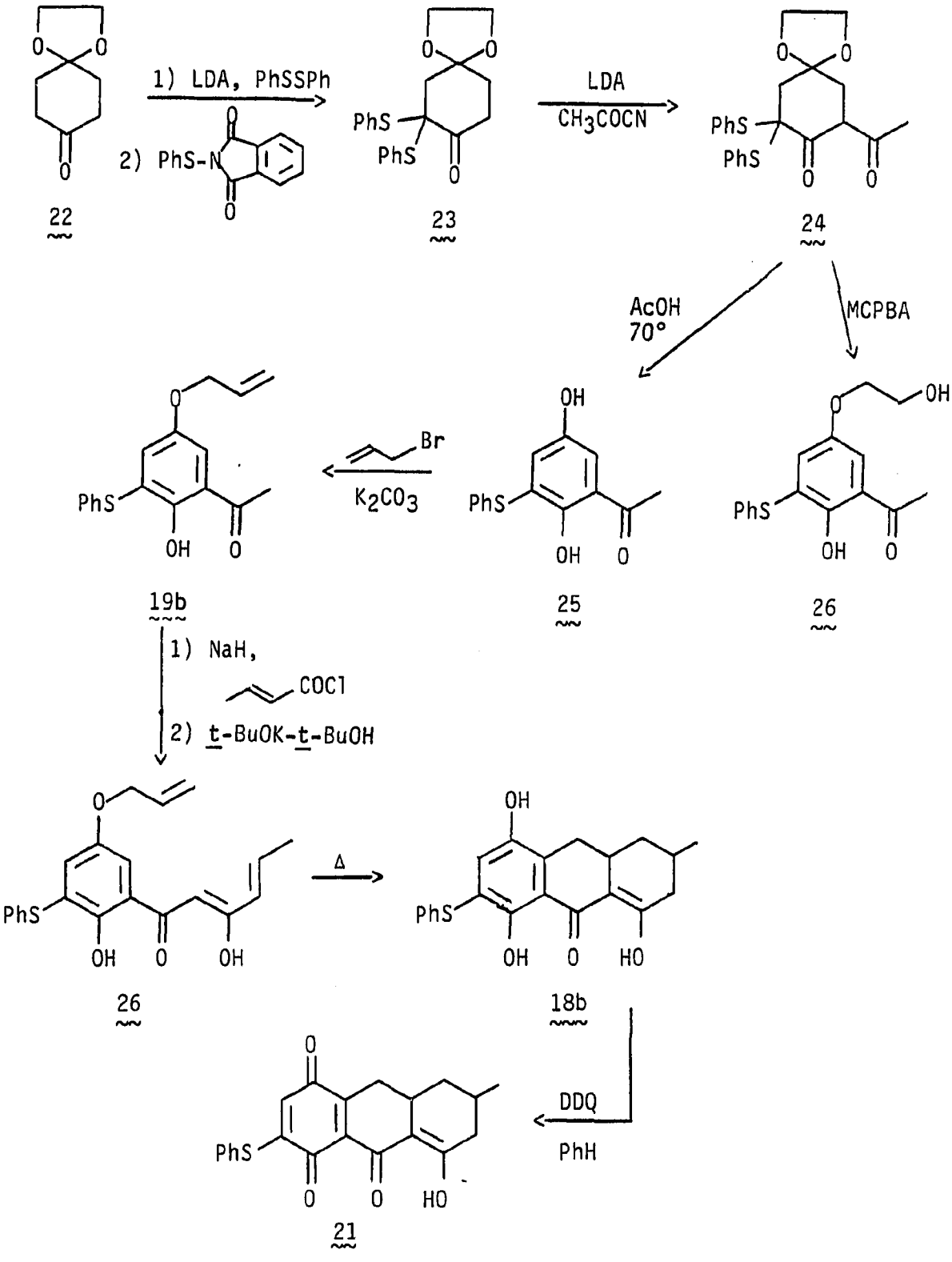
b: X = SPh



In order to ascertain which quinone was formed, an alternative route to 21 was devised later. It was reasoned that once the compound 19b which already possesses the phenylthio substituent on the aromatic ring could be prepared, conversion of 19b to 21 would be achieved utilizing the chemistry described in Scheme 2.

The synthesis of hydroquinone 25 presented some difficulty since no readily available aromatic starting materials could be obtained which allow elaboration to 25. After considerable experimentation, a four step synthesis of 25 was eventually developed starting with commercially available 1,4-cyclohexanedione monoketal 22. Conversion of 22 to 23 followed by the condensation of anion of 23 with CH_3COCN at 0°C furnished 24 which, upon exposure to acid, yielded hydroquinone 25. It is interesting to note that reaction of 24 with MCPBA at 0°C produced

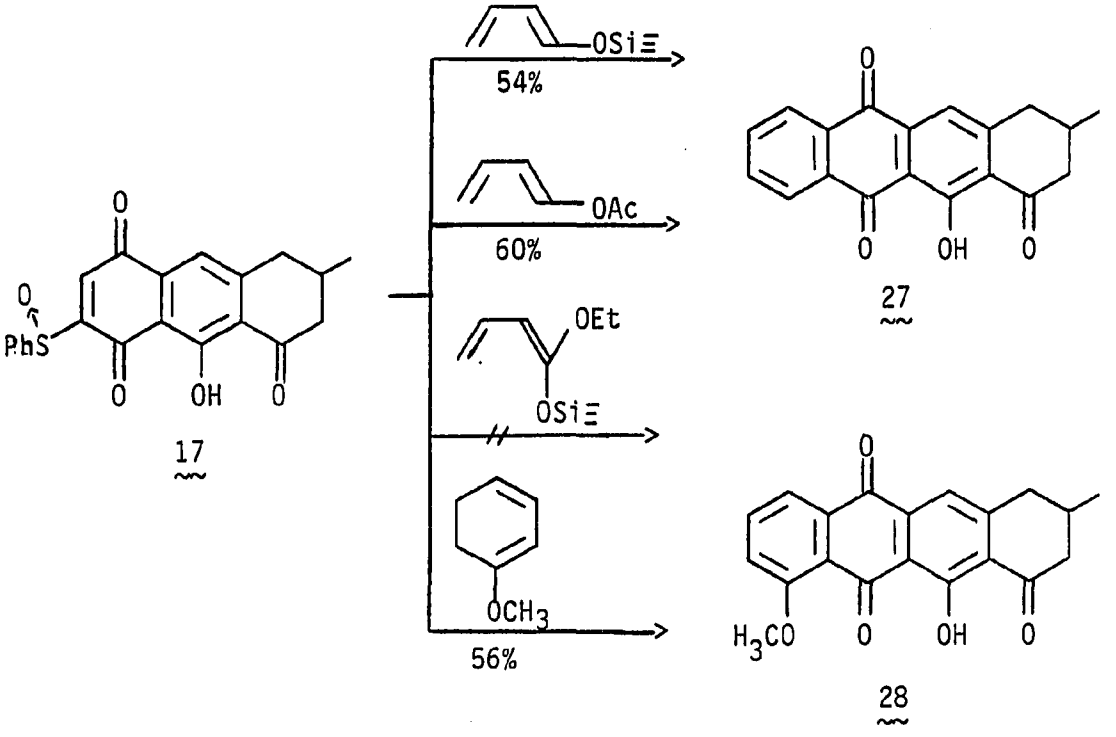
Scheme 2


1) LDA, PhSSPh
2) PhS-N
LDA
CH3COCN
AcOH
70°
MCPBA
Br
K2CO3
1) NaH,
COCl
2) t-BuOK-t-BuOH
Δ
DDQ
PhH
PhS
OH
HO
22
23
24
19b
25
26
18b
21

directly the aromatic compound 26 in good yield instead of the corresponding sulfoxide or elimination product. The hydroquinone 25 could be transformed into the tricyclic quinone 21 in four additional steps as outlined in Scheme 2.

It was found that IR and NMR spectra of the quinone 21 obtained above were identical with those of the compound prepared previously via benzenethiol addition to 20, thus confirming the regiochemistry of 21.

Having established a regioselective route to 21, we next investigated the Diels-Alder behavior of quinone sulfoxide 17 with several dienes. Cycloaddition of 17 with either 1-trimethylsilyloxy-1,3-butadiene or 1-acetoxy-1,3-butadiene afforded the expected product anthracyclinone 27 in 54-60% yield.



In an effort to prepare 4-methoxyanthracyclinone 28, we initially reacted 17 with 1-ethoxy-1-trimethylsilyloxy-1,3-butadiene. Unfortunately, this reaction failed to afford the desired Diels-Alder adduct and resulted in intractable tars. Alternatively, we found that with 1-methoxy-1,3-cyclohexadiene, anthraquinone 28 could be obtained as a single product. The assigned regiochemistry of 28 was based upon the polarizing effect of the sulfoxide group. Efforts to prepare nogalamycin are currently in progress.

In summary, the use of quinone sulfoxide represents a viable alternative to existing methodology. The ease of preparation combined with the facile elimination of phenylsulfenic acid makes this a versatile synthetic method. Furthermore, the strategy described herein may be applicable to the regioselective syntheses of 11-deoxyanthracyclines and related compounds, thus allowing the preparation of new analogs with better pharmacological properties.

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 a nitrogen 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. 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.).

General Procedure for the Diels-Alder Reaction of Quinone Sulfoxides

A solution of the diene (2-3 equiv) and quinone sulfoxide (1 equiv) was dissolved in the solvent (1 M with regard to the sulfoxide) and stirred at the temperature specified below until TLC indicated that the sulfoxide was gone. The solvent was removed in vacuo and the crude product was chromatographed on silica gel to afford pure product.

Entries 1-3, 7 and 8: refluxing carbon tetrachloride, entries 4 and 5: refluxing toluene, entry 6: carbon tetrachloride at room temperature (see Table 1).

1-Acetoxy-4-methyl-1,4-dihydro-9,10-anthraquinone (5): 60 MHz ^{1}H NMR ($CDCl_3$) δ 1.28 (d, J = 7 Hz, 3 H), 1.98 (s, 3 H), 3.40-4.04 (m, 2 H), 4.24 (d, 2 H, J = 4 Hz), 5.70-5.92 (m, 2 H), 7.52-7.80 (m, 2 H), 7.84-8.12 (m, 2 H); IR ($CDCl_3$) 2990, 1740, 1668, 1550, 1231, 1205, 1140 cm^{-1}; MS m/e 165, 209, 224, 236, 254, 266 (M^+-CH_2O); high resolution mass spectrum for $C_{17}H_{14}O_3$ (M^+-CH_2O) requires 266.09429, determined 266.09398.

Anthracene adduct 6: 60 MHz NMR ($CDCl_3$) δ 6.03 (s, 2 H), 7.35-7.82 (m, 4 H), 7.35-7.82 (m, 4 H), 7.90-8.30 (m, 4 H); MS m/e 334 (M^+).

Methoxyfuran adduct 7: 300 MHz NMR ($CDCl_3$) δ 3.96 (s, 3 H), 5.48 (d, J = 2.0 Hz, 1 H), 7.06 (s, 1 H), 7.62 (d, 1 H, J = 2.0 Hz), 7.68-7.78 (m, 2 H), 8.03-8.15 (m, 2 H); MS m/e 189, 204, 239, 254; high resolution mass spectrum for $C_{15}H_{10}O_4$ requires 254.0579, determined 254.0573.

1,4-Tetrahydro-9,10-anthraquinone (14): 300 MHz NMR ($CDCl_3$) δ 3.22 (br s, 4 H), 5.88 (br s, 2 H), 7.66-7.78 (m, 2 H), 8.03-8.13 (m, 2 H); IR

($CDCl_3$) 3037, 1650, 1590, 1285, 1163 cm^{-1}; MS m/e 77, 105, 165, 181, 210 (M^+).

Naphthoquinone 20

To a stirred solution of 0.583 g (2.24 mmol) of the tricyclic β-diketone 18a in 20 ml of dry benzene was added at 5°C 1.12 g (4.93 mmol) of 2,3-dichloro-4,5-dicyanobenzoquinone. The reaction mixture was stirred at room temperature for 8 hours. The resulting orange-red suspension was filtered, and the residue was washed thoroughly with the cold methylene chloride. The filtrate and washed were combined, dried, and concentrated in vacuo. Flash chromatography on silica gel eluting with methylene chloride afforded 0.40 g (70%) of quinone 20 as a yellow solid: mp 172-173°C (decomposition); 300 MHz ^1H NMR ($CDCl_3$) δ 1.18 (d, 3 H, J = 6.0 Hz), 2.30-2.77 (m, 3 H), 2.83 (d, 1 H, J = 15.9 Hz), 3.13 (dd, 1 H, J = 16.8 Hz, J = 3.0 Hz), 6.93 (s, 2 H), 7.46 (s, 1 H), 13.73 (s, 1 H): IR ($CDCl_3$) 2975, 1659, 1630 (sh), 1590, 1340, 1220, 1102, 840 cm^{-1}; MS m/e 130, 158, 214, 241, 256 (M^+); high resolution mass spectrum for $C_{15}H_{12}O_4$ requires 256.07356, determined 256.07381.

Naphthoquinone Sulfide 21

To a cold suspension of 280 mg (1.09 mmol) of the quinone 20 in 20 ml of ethanol was added 145 mg (1.31 mmol) of benzenethiol in ethanol (2 ml), and the mixture was stirred at ambient temperature for 12 hours. The resulting brown solution was treated with 0.21 g of potassium dichromate in 1.5 ml of water and 0.15 ml of sulfuric acid and stirred for 2 hours at room temperature. To this orange solution was added 20 ml

of water, and the yellow solids which formed were filtered, washed with water, and dried *in vacuo* to provide 290 mg (73%) of **21**: 300 MHz ^{1}H NMR ($CDCl_3$) δ 1.73 (d, 1 H, J = 6.0 Hz), 2.31-2.51 (m, 2 H), 2.73 (dd, 1 H, J = 16.8 Hz, J = 10.5 Hz), 2.84 (dd, 1 H, J = 13.5 Hz, J = 1.8 Hz), 3.09 (dd, 1 H, J = 15.9 Hz, J = 3.6 Hz), 6.04 (s, 1 H), 7.04 (s, 1 H), 7.43-7.60 (m, 5 H), 13.76 (s, 1 H); IR ($CDCl_3$) 3065, 2888, 1670, 1640 (sh), 1601, 1578, 1380, 1220, 1132 cm^{-1}; MS m/e 110, 218, 287, 335, 364 (M^+); high resolution mass spectrum for $C_{21}H_{16}O_4S$ requires 364.09259, determined 364.09241.

Naphthoquinone Sulfoxide **17**

To a solution of the quinone sulfide (232 mg, 0.637 mmol) in 20 ml of methylene chloride at 0°C was added *meta*-chloroperbenzoic acid (120 mg, 0.69 mmol), and the mixture was stirred at room temperature for 1 hour. The solvent was removed *in vacuo* and the residue crystallized at 0°C from hexane-methylene chloride to afford 225 mg (93%) of **17** as yellow needles: mp 162-164°C; 300 MHz ^{1}H NMR ($CDCl_3$) δ 1.19 (d, 3 H, J = 5.9 Hz), 2.29~3.18 (m, 5 H), 7.28-8.19 (m, 7 H), 13.83 (s, 1 H); IR ($CDCl_3$) 1665, 1595, 1370, 1213, 1123, 1076, 1045 cm^{-1}: MS m/e 125, 141, 214, 260, 287, 364, 380 (M^+); high resolution mass spectrum for $C_{21}H_{16}O_5S$ requires 380.0718, determined 380.0715.

4,4'-Ethylenedioxo-2-phenylthiocyclohexanone (**22**)

To a stirred solution containing 10 ml of dry THF and 1.26 ml (9.0 mmol) of diisopropylamine at 0°C was added 3.55 ml of n-butyllithium (2.48 M in hexane, 8.8 mmol). After 15 minutes, the solution was cooled

to -23°C and 0.624 g (4.0 mmol) of 1,4-cyclohexanedione monoketal in THF (1 ml)-HMPA (6 ml) was added dropwise over a period of 10 minutes. The solution was allowed to warm to 0°C over 1 hour and stirred at room temperature for 30 minutes. The reaction mixture was cooled to 0°C, and a solution of diphenyldisulfide (2.25 g, 9.0 mmol) in 3 ml of THF was added. The solution was allowed to warm to room temperature over 1 hour and then stirred for an additional 1 hour. The resulting dark solution was poured into saturated aqueous ammonium chloride (30 ml) and extracted with ethyl ether. The combined organic phase was washed with brine and dried. The solvents were removed in vacuo and the residue chromatographed on silica gel eluting with 3:1 hexane:ethyl acetate to provide 0.96 g (91%) of 22 as a light yellow solid: mp 68-69°C; 60 MHz ^{1}H NMR ($CDCl_3$) δ 1.78-2.81 (m, 6 H), 4.01 (br s, 4 H), 4.02-4.10 (m, 1 H), 7.21-7.63 (m, 5 H); IR ($CDCl_3$) 3140, 2980, 1709, 1470, 1375, 1112 cm^{-1}; high resolution mass spectrum for $C_{14}H_{16}O_3S$ requires 264.08202, determined 264.08213.

4,4'-Ethylenedioxo-2,2-diphenylthiocyclohexanone (23)

To a stirred solution of 22 (4.98 g, 18.84 mmol) and N-(phenythio)-phthalimide (4.56 g, 18.84 mmol) at room temperature was added 2.89 ml (20.7 mmol) of triethylamine. The reaction mixture was heated at reflux for 12 hours. After the mixture cooled, the white precipitate of phthalimide was filtered off, and the filtrate was concentrated in vacuo. The residue was crystallized from absolute ethanol to afford 4.5 g (71%) of pure 23 as light yellow needles: mp 145-145.5°C; 300 MHz ^{1}H NMR ($CDCl_3$) δ 2.04 (t, 2 H, J = 6.6 Hz), 2.40 (br s, 2 H), 2.99 (t, 2 H, J =

7.2 Hz), 3.96 (br s, 4 H), 7.29-7.39 (m, 5 H); IR ($CDCl_3$) 3140, 3050, 2978, 1700, 1468, 1262, 1105, 1058 cm^{-1}; high resolution mass spectrum for $C_{20}H_{20}O_3S_2$ requires 372.08540, determined 372.08588.

2-Acetyl-4,4'-ethylenedioxo-6,6-diphenythiocyclohexanone (24)

To a stirred solution of 3.20 mmol of LDA in 10 ml of dry THF at -23°C was added a solution of 1.0 g (2.70 mmol) of the ketone 23 in 2 ml of dry THF. After 20 minutes 0.23 ml (3.20 mmol) of pyruvonitrile in 2 ml of the THF was added rapidly, and the reaction mixture was allowed to warm to room temperature over 1 hour. The resulting dark solution was then poured into 30 ml of ice water, acidified with 2N HCl, and extracted with ethyl ether. The organic extracts were combined, washed with brine, and dried. The solvents were removed in vacuo and the residue chromatographed on silica gel eluting 3:1 hexane:ethyl acetate to provide 0.71 g (64%) of 24 as a light yellow oil: 300 MHz ^1H NMR ($CDCl_3$) δ 2.10 (s, 3 H), 2.24 and 2.41 (s, 2 H), 3.61-4.0 (m, 3 H), 7.28-7.42 (m, 5 H), 7.59-7.63 (m, 5 H); IR (neat) 3058, 2880, 1710, 1580, 1440, 1260, 1120, 1050, 950 cm^{-1}.

2-Hydroxy-5-(2-hydroxyethyloxy)-3-phenythioacetophenone (26)

To a solution of 24 (77 mg, 0.186 mmol) in 5 ml of methylene chloride at 0°C was added meta-chlorobenzoic acid (40 mg, 0.230 mmol), and the mixture was stirred at 0°C for 1 hour. The reaction mixture was diluted with 15 ml of methylene chloride, washed with 10% sodium bicarbonate solution and water, and dried. The solvent was removed in vacuo and the residue chromatographed on silica gel 2:1 hexane:ethyl acetate to afford

40.7 mg (72%) of 26 as a yellow oil: 300 MHz ^{1}H NMR ($CDCl_3$) δ 2.63 (s, 3 H), 3.78-3.99 (m, 4 H), 6.85 (d, 1 H, J = 3.0 Hz), 7.11 (d, 1 H, J = 3.0 Hz), 7.32-7.47 (m, 5 H); IR (neat) 3600, 3142, 1638, 1602, 1580, 1310, 1040 cm^{-1}; MS m/e 111, 140, 167, 260, 304 (M^+).

2,5-Dihydroxy-3-phenylthioacetophenone (25)

A solution of 1.15 g (2.78 mmol) of 24 in 10 ml of 4:1 acetic acid/water containing 2 drops of sulfuric acid was heated at 70°C for 1 hour and then cooled to room temperature. The reaction mixture was poured into 20 ml of saturated sodium bicarbonate, extracted with ethyl acetate, and dried. The solvent was removed in vacuo, and the residue chromatographed on silica gel eluting 1:1 hexane:ethyl acetate to afford 607 mg (84%) of pure 25 as a yellow solid: mp 195-197°C; 300 MHz ^{1}H NMR ($CDCl_3$) δ 2.61 (s, 3 H), 4.72 (s, 1 H), 6.71 (d, 1 H, J = 3.0 Hz), 7.07 (d, 1 H, J = 3.0 Hz), 7.34-7.49 (m, 5 H), 12.43 (s, 1 H); IR ($CDCl_3$) 3580, 3140, 1640, 1460, 1375, 1090 cm^{-1}; high resolution mass spectrum for $C_{14}H_{12}O_3S$ requires 260.05072, determined 260.05066.

5-Allyloxy-2-hydroxy-3-phenylthioacetophenone (19b)

To a stirred solution of 25 (240 mg, 0.92 mmol) in 10 ml of acetone at room temperature was added anhydrous potassium carbonate (117 mg, 0.97 mmol) followed by freshly distilled allyl bromide (0.10 ml, 1.0 mmol). The mixture was heated at reflux for 8 hours. The resulting dark solution was poured into 20 ml of cold water, acidified with 6N HCl to pH 5, and extracted with ethyl acetate. The combined extracts were washed with brine, dried, and concentrated in vacuo. Flash chromatography on

silica gel eluting with 3:1 hexane:ethyl acetate afforded 110 mg (40%) of 19b as a yellow solid, yellow needles from ethanol: mp 92-92.5°C; 300 MHz ^{1}H NMR ($CDCl_3$) δ 2.61 (s, 3 H), 4.39 (d, 2 H, J = 5.4 Hz), 5.23-5.34 (m, 2 H), 5.89-6.02 (m, 1 H), 6.86 (d, 1 H), J = 3.0 Hz), 7.10 (d, 1 H, J = 3.0 Hz), 7.29-7.47 (m, 5 H), 12.47 (s, 1 H); IR ($CDCl_3$) 3060, 1630, 1600, 1430, 1360, 1230, 1170, 1020 cm^{-1}; MS m/e 185, 241, 259, 300; high resolution mass spectrum for $C_{17}H_{16}O_3S$ requires 300.08202, determined 300.08233.

3-Hydroxy-1-[5-(allyloxy)-2-hydroxy-3-phenylthio]-hexa-2,4-dien-1-one (26)

To a suspension of 30 mg (0.62 mmol) of sodium hydride (hexane-washed) in 7 ml of THF at 0°C was added 170 mg (0.567 mmol) of 19b in 2 ml of THF. After 10 minutes 65 mg (0.62 mmol) of crotonyl chloride was added, and the resulting mixture was stirred at 0°C for 20 minutes. The tert-butoxide/tert-butanol was then added in one portion and stirring continued at 0°C for 1 hour. The reaction mixture was poured into cold water, acidified with 6N HCl to pH 6, and extracted with ethyl acetate. The organic extracts were combined, washed with brine, dried, and concentrated in vacuo. Flash chromatography on silica gel eluting 5:1 hexane:ethyl acetate provided 148 mg (71%) of 25: 300 MHz ^{1}H NMR ($CDCl_3$) δ 1.93 (d, 3 H, J = 5.9 Hz), 4.39 (d, 2 H, J = 5.5 Hz), 5.28-5.38 (m, 2 H), 5.88-6.04 (m, 1 H), 6.07 (s, 1 H), 6.72-7.48 (m, 9 H), 12.39 (s, 1 H), 14.51 (s, 1 H); IR ($CDCl_3$) 3250-2870 (br), 1640, 1590, 1430, 1370, 1240, 1165, 1040, 970 cm^{-1}.

Tricyclic β-diketone 18b

A solution of the β-diketone 25 (100 mg, 0.271 mmol) in 3 ml of benzene containing a small crystal of hydroquinone was deoxygenated at -78°C and sealed in a glass tube. The solution was heated at 230°C for 16 hours. The tube was then cooled to -78°C and opened. The solvent was removed in vacuo, and the residue chromatographed on silica gel eluting 2:1 hexane:ethyl acetate to yield 68 mg (68%) of 18b as an orange solid: mp 210-211°C; 300 MHz ^{1}H NMR ($CDCl_3$) δ 1.04 (d, 3 H, J = 7.2 Hz), 1.52-2.90 (m, 7 H), 3.08 (dd, 1 H, J = 16.8 Hz, J = 3.8 Hz), 4.38 (s, 1 H), 6.80 (s, 1 H), 7.25-7.41 (m, 5 H), 12.19 (s, 1 H), 14.53 (s, 1 H); IR ($CDCl_3$) 3480, 2965, 1610, 1575, 1460, 1320, 1260, 1205 cm^{-1}; high resolution mass spectrum for $C_{21}H_{20}O_4S$ requires 368.18024, determined 368.10851.

Anthraquinone 27

A solution of 50 mg (0.13 mmol) of the quinone sulfoxide 17 and 44 mg (0.39 mmol) of 1-acetoxy-1,3-butadiene in 5 ml of carbon tetrachloride was heated at reflux for 1 hour. The reaction mixture was cooled to room temperature, and the solvent was removed under reduced pressure. The crude product was purified by chromatography on silica gel eluting 3:2 hexane:ethyl acetate to afford 27 mg (60%) of 27 as an orange solid: 300 MHz ^{1}H NMR ($CDCl_3$) δ 1.16 (d, 3 H, J = 5.9 Hz), 2.23-3.21 (m, 5 H), 7.57 (s, 1 H), 7.63~7.78 (m, 2 H), 8.12-8.26 (m, 2 H), 13.57 (s, 1 H); IR ($CDCl_3$) 1665, 1630 (sh), 1587, 1348, 1255, 1012 cm^{-1}; MS m/e 152, 180, 208, 264, 291, 306 (M^+); high resolution mass spectrum for $C_{19}H_{14}O_4$ requires 306.0892, determined 306.0900.

Anthraquinone 28

A solution of 57 mg (0.15 mmol) of the quinone sulfoxide 17 and 50 mg (0.45 mmol) of 1-methoxy-1,3-cyclohexadiene in 5 ml of xylene was heated at 80°C for 1 hour and then refluxed for 20 minutes. The reaction mixture was cooled to room temperature, and the solvent was removed under reduced pressure. Flash chromatography on silica gel eluting 2% ethyl acetate in methylene chloride provided 27.2 mg (56%) of 28 as a yellow-orange solid: mp 242-245°C; 300 MHz ^{1}H NMR ($CDCl_3$) δ 1.17 (d, 3 H, J = 6.0 Hz), 2.37-2.48 (m, 2 H), 2.71-2.78 (m, 1 H), 2.82 (d, 1 H, J = 13.2 Hz), 3.12 (d, 1 H, J = 16.3 Hz), 4.05 (s, 3 H), 7.37 (d, 1 H, J = 8.7 Hz), 7.57 (s, 1 H), 7.72 (t, 1 H, J = 8.1 Hz), 7.88 (d, 1 H, J = 8.4 Hz), 14.14 (s, 1 H): IR ($CDCl_3$) 2970, 1688, 1620, 1580, 1211, 1030, 960 cm^{-1}; high resolution mass spectrum for $C_{20}H_{16}O_5$ requires 336.09978, determined 336.09938.

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OVERALL SUMMARY

The total synthesis of anthracycline antibiotics is believed to be among the most promising subjects for the development of new drugs for the treatment of human cancers. It was the purpose of this research to develop novel synthetic approaches to 11-deoxyanthracyclines.

Part I describes the successful total synthesis of 11-deoxydaunomycinone and 4-demethoxy 11-deoxydaunomycinone by a sequence involving an acyl transfer reaction followed by a tandem Claisen-Diels-Alder reaction. Oxidation of the resulting β-diketone with DDQ provides the tricyclic naphthoquinone which contains functionality well suited for the synthesis of 11-deoxyanthracyclines with different D ring substitution. Subsequent Diels-Alder reaction with either 1-methoxy-1,3-cyclohexadiene or 1-trimethylsilyloxy-1,3-butadiene produces adducts which can be transformed into 11-deoxydaunomycinone and its 4-demethoxy analogue.

Part II describes the direct and operationally convenient synthesis of linear polycyclic quinones via the Diels-Alder reaction of quinone sulfoxides. The mild conditions required to effect both Diels-Alder reaction and elimination of phenylsulfinic acid represent a useful feature of this reaction. The utility of this method is demonstrated further by the regiospecific preparation of the tricyclic quinone sulfoxide and its use for the construction of the tetracyclic framework of the 11-deoxyanthracycline nucleus.

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