1981

Studies in anthracycline synthesis

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STUDIES IN ANTHRACYCLINE SYNTHESIS

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Studies in anthracycline synthesis

by

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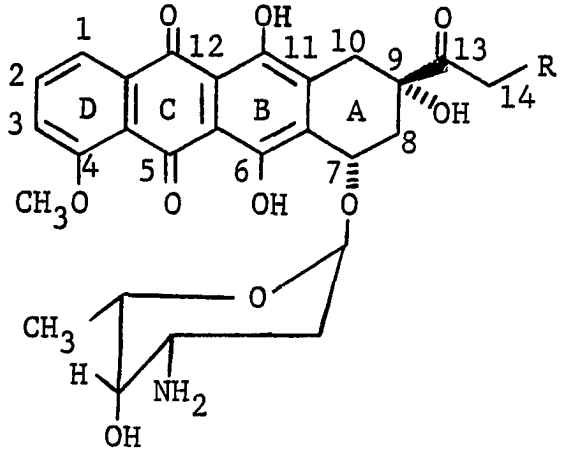
INTRODUCTION

During the last ten years, adriamycin (1) and daunomycin (2) have become major components in the arsenal of chemotherapeutic agents for the treatment of a wide range of cancers. The less toxic 11-deoxyanthracyclines have recently been discovered and may prove to be even more effective anticancer drugs than adriamycin and daunomycin. Aclacinomycin A (3) is the most promising member of this new group of anthracyclines. This manuscript will detail the results of a program to develop a total synthesis of the aglycone of aclacinomycin A and a total synthesis of a structurally related compound, ekatetrone (5).

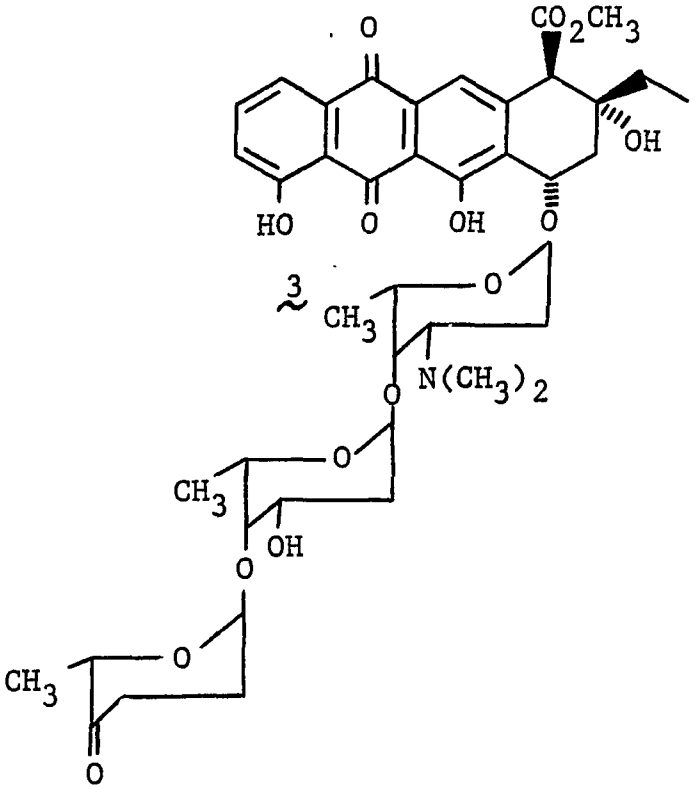
HISTORICAL

The search for effective chemical agents for the treatment of a wide range of cancers has led investigators to study the antitumor properties of a variety of naturally occurring compounds. This search has resulted in the discovery of several very effective classes of naturally occurring antitumor compounds. The anthracycline antitumor antibiotics are among the most active compounds discovered in the last ten years. Adriamycin 1 and daunomycin 2, also known as daunorubicin, have proven to be very effective and are widely used clinically. Efforts to develop even more active antitumor agents with fewer side effects led to the discovery of other anthracyclines, among which aclacinomycin A 3 appears to be of special interest. Aclacinomycin A, when compared to adriamycin and daunomycin, has equally high antitumor activity and reduced toxic side effects. The lower cardiotoxicity of aclacinomycin A is especially important.

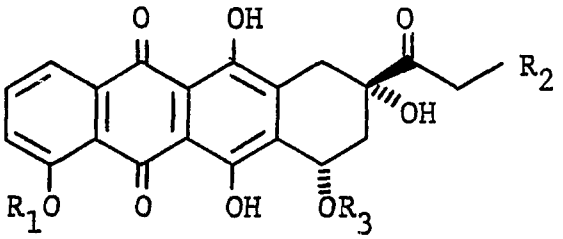


1 R = OH

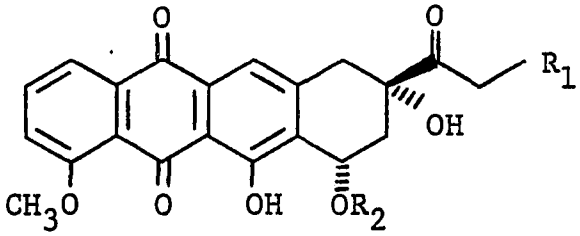
2 R = H



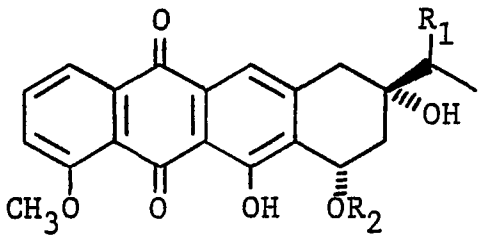
Group I



	R_1	R_2	R_3
Daunomycin	CH_3	H	daunosamine
Adriamycin	CH_3	OH	daunosamine
Carminomycin	H	H	daunosamine

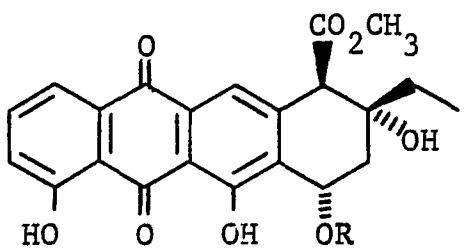


	R_1	R_2
11-Deoxydaunomycin	H	daunosamine
11-Deoxyadriamycin	OH	daunosamine



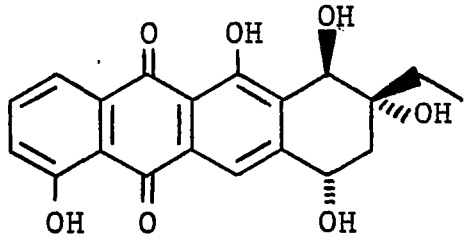
	R_1	R_2
11-Deoxy-13-dihydrodaunomycin	OH	daunosamine
11-Deoxy-13-deoxydaunomycin	H	daunosamine

Group II



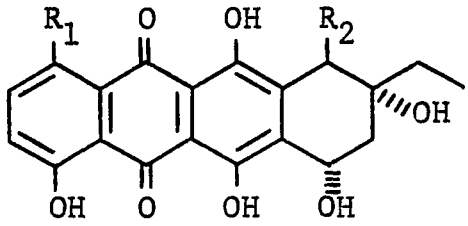
	R
Aklavinone	H
Aklavin	Rhodosamine
Aclacinomycin A	Rhodosamine + 2-Deoxy-L-fucose + L-Cinerulose
Aclacinomycin B	Rhodosamine + 2-Deoxy-L-fucose + Cinerulose B
Aclacinomycin Y	Rhodosamine + 2-Deoxy-L-fucose + Amicetose

Group III



Citromycins

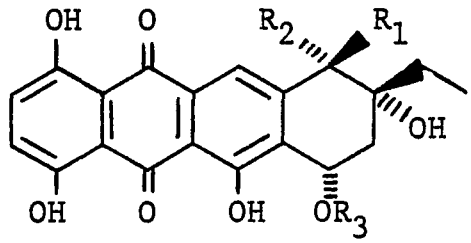
Group IV



Rhodomycins R_1 = H or OH

R_2 = CO_2CH_3 or OH

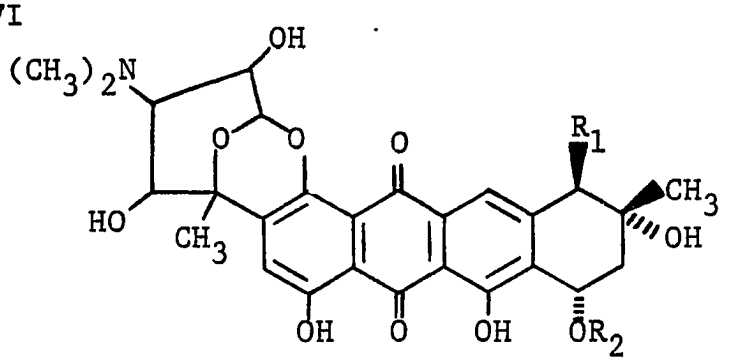
Group V



	R_1	R_2	R_3
Pyrromycin	CO_2CH_3	H	Rhodosamine
Cinerubin A	CO_2CH_3	H	Rhodosamine + 2-Deoxy-L-fucose + L-Cinerulose
Cinerubin B	CO_2CH_3	H	Rhodosamine + 2-Deoxy-L-fucose + Cinerulose B
Marcellomycin	CO_2CH_3	H	Rhodosamine + 2-Deoxy-L-fucose + 2-Deoxy-L-fucose
Collinemycin	H	CO_2CH_3	Rhodosamine + 2-Deoxy-L-fucose
Mimimycin	H	CO_2CH_3	Rhodosamine + 2-Deoxy-L-fucose + 2-Deoxy-L-fucose

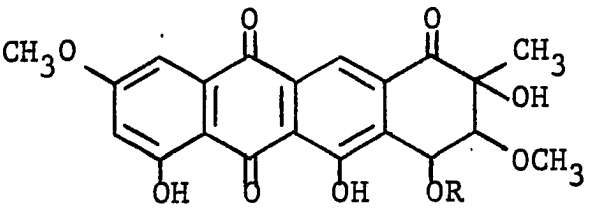
	R_1	R_2	R_3
Rudolphomycin	CO_2CH_3	H	Rhodosamine + 2-Deoxy-L-fucose + Rednose
Alcindoromycin	CO_2CH_3	H	Monodemethylrhodosamine + 2-Deoxy-L-fucose + 2-Deoxy-L-fucose
10-Descarbomethoxy Marcellomycin	H	H	Rhodosamine + 2-Deoxy-L-fucose + 2-Deoxy-L-fucose
10-Descarbomethoxy Rudolphomycin	H	H	Rhodosamine + 2-Deoxy-L-fucose + Rednose
Rhodorubin A	CO_2CH_3	H	Rhodosamine + 2-Deoxy-L-fucose + Rhodinose
Rhodorubin B	CO_2CH_3	H	Rhodosamine + 2-Deoxy-L-fucose + D-Cinerulose
Rhodorubin G	CO_2CH_3	H	Rhodosamine + 2-Deoxy-L-fucose + Amicetose

Group VI



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

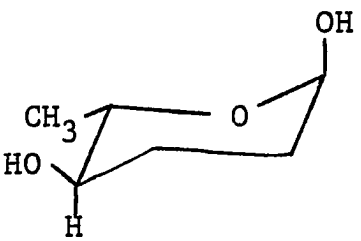
Group VII



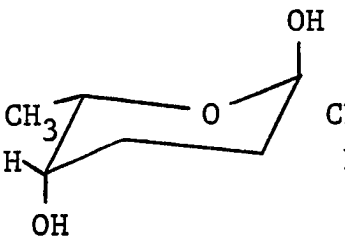
R

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

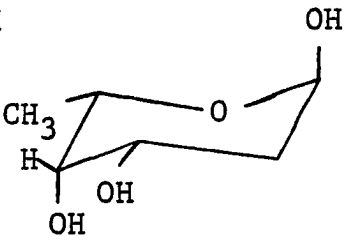
Some sugars found in anthracyclines:



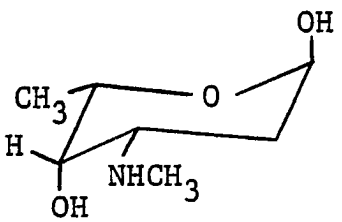
Amicetose



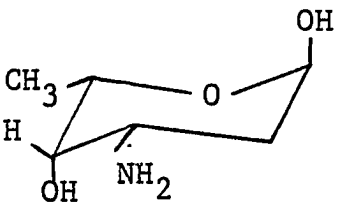
Rhodinose



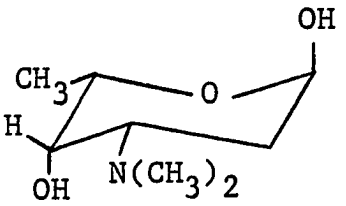
2-Deoxy-L-fucose



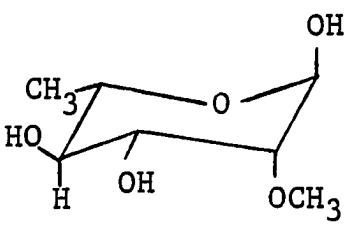
Monodemethylrhodosamine



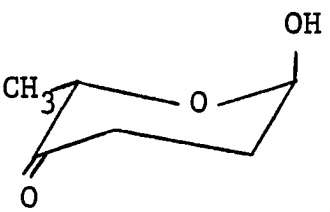
Daunosamine



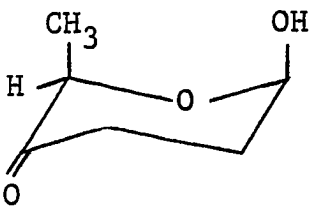
Rhodosamine



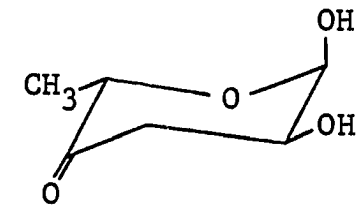
2-O-Methyl-L-rhamnose



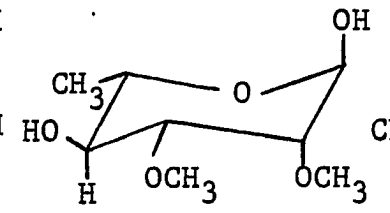
L-Cinerulose



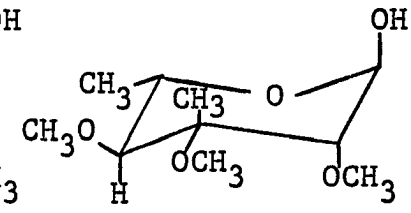
D-Cinerulose



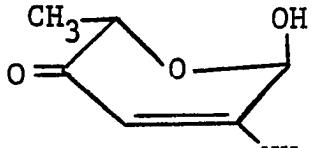
Cinerulose-B



2,4-Di-O-methyl-L-rhamnose



Nogalose



Rednose

Several dozen naturally occurring anthracyclines have been isolated and many synthetic analogues have been developed. The biochemical and medical aspects of these compounds have been covered in several excellent reviews (1-6). The most important aspects of structure and activity relationships between the different anthracyclines will be summarized here and, along with more recent information, the increasing importance of the 11-deoxy anthracyclines related to aclacinomycin will be shown.

The anthracyclines can be divided into seven groups based on the substitution pattern found on the aglycone portion of the molecule. Historically, compounds in Group IV having the rhodomycinone aglycone were the first to be isolated and have their structures determined (7). The rhodomycins were found to be highly toxic compounds (7).

Cinerubin A and cinerubin B were first isolated in 1959. They were found to be cytotoxic and have antibacterial and antitumor properties, but were also found to be highly toxic in mice and rats (8).

Daunomycin, the first clinically effective anthracycline, was discovered in 1963 (9a). While for most uses it proved to be highly toxic, daunomycin was especially effective for treatment of acute leukemias (9b).

The structure of adriamycin was determined in 1969 (10a) and soon afterward it was shown to be less toxic than daunomycin and active against a broader spectrum of tumors (10b). Adriamycin is effective against breast cancer, osteogenic sarcoma, cancers of the bladder, lung, thyroid and ovary, Wilms' tumor, neuroblastoma, Hodgkin's disease and other lymphomas and acute leukemias. Many solid tumors which respond to adriamycin treatment are often unresponsive to other chemotherapy (1)..

Adriamycin and daunomycin were isolated from a mutant strain of Streptomyces peucetius. Because of their wide range of anticancer activity, especially the effectiveness of adriamycin against solid tumors, a study of other Streptomyces strains has led to the discovery of dozens of new anthracyclines.

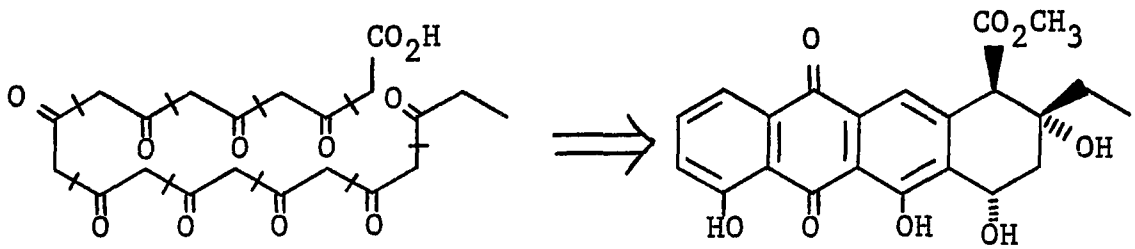
Workers at Bristol Laboratories isolated a series of anthracyclines based on pyrromycinone (Group V) from the

Bohemic acid complex (11). It is the practice at Bristol to name antitumor antibiotic complexes after operas. Compounds isolated from the complex are given names based on characters in the libretto. A number of compounds based on nogalomycinone (12) (Group VI) and steffimycinone (13) (Group VII) were isolated by other workers. Very recently Arcamore and coworkers isolated compounds in the 11-deoxy adriamycin and 11-deoxydaunomycin series (14).

Probably the most important discovery came in 1975, when the aclacinomycins (Group II) were isolated and their structures determined (15). Aclacinomycins A and B were isolated from Streptomyces galileus MA144-M1. Aclacinomycin A was found to be highly active against L1210 and P388 leukemia, Ehrich ascites tumor, rat hepatomas, S-180 solid tumor, CD mammary carcinoma, colon 38 carcinoma and moderately or weakly active against several other cancers (4). It was found to be ten times less cardiotoxic than adriamycin in hamsters and rabbits (16).

The structure of aclacinomycin A was determined by mild acid hydrolysis to give aklavinone, a naturally occurring substance whose structure had previously been determined (17), and three sugars. The sugars were identified by TLC (thin layer chromatography) comparison with the known sugars in cinerubin A.

The anthracyclines containing a two carbon side chain at C-9 are thought to arise biosynthetically from the combination of one propionate and nine acetate units, giving a polyketide intermediate which is common to all of the compounds (18). The anthracyclines with a one carbon side



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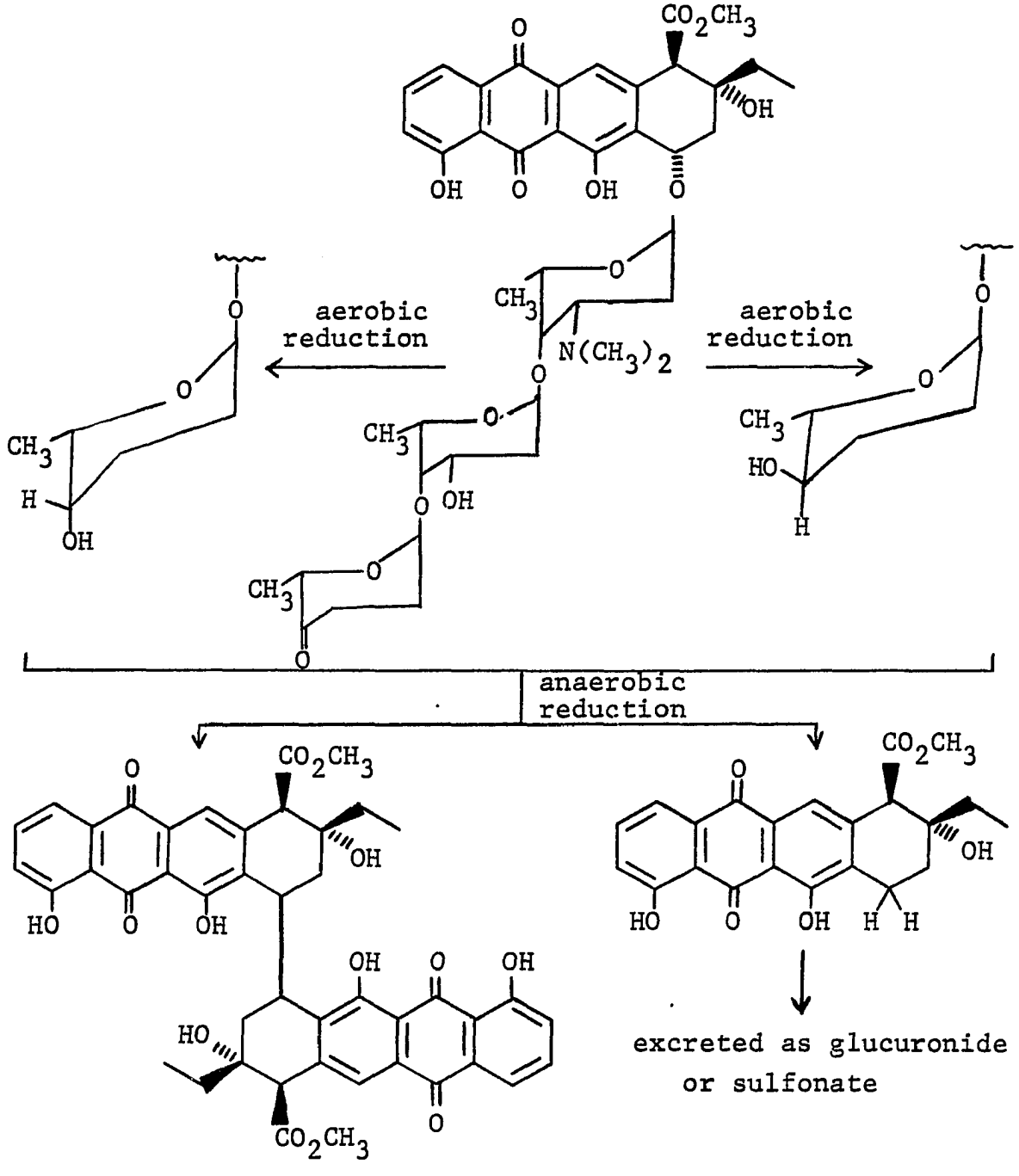
chain at C-9 must arise from the combination of ten acetate units. Labelling studies and use of mutated strains of Streptomyces indicate that aklavinone 4 is a common intermediate in the biosynthesis of the other anthracyclines (5). For example, by various oxidations and decarbalkoxylation, daunomycinone can be obtained from aklavinone.

The metabolism of aclacinomycin A has been studied using rat liver homogenates (4). Under aerobic conditions, the ketone of the cinerulose sugar becomes reduced. Under anaerobic conditions, reductive cleavage of the glycosidic linkage takes place. The dimeric reduction product has also been isolated from the fermentation broth of Streptomyces galileus (19). Some of the metabolic products or

derivatives of them have been isolated during animal testing with aclacinomycin A (4).

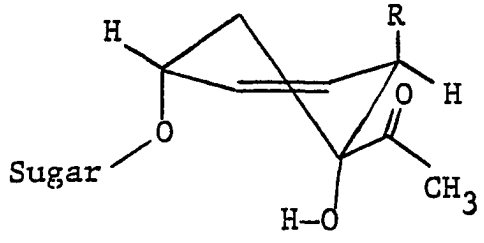


The mechanism of action of the anthracyclines has been studied in great detail. The antitumor activity is thought to arise mainly from a binding interaction between the anthracycline and DNA (deoxyribonucleic acid). This provides a unique circumstance. Due to the very detailed knowledge of the structure of DNA as a biological receptor, a very good model for DNA-anthracycline binding can be proposed.

When isolated double stranded DNA and an anthracycline are mixed in solution, very obvious changes occur in the physical and spectral properties of both compounds (20). This information, in combination with data from X-ray diffraction studies (21) of the DNA-anthracycline complex, clearly indicates that the anthracycline intercalates between the base pairs of the DNA helix.

The X-ray structure determination of daunomycin and NMR analyses (22) show that the A ring exists in a half chair conformation. This completes the information needed to propose a detailed model of the binding interaction. Extensive overlap between the planar tricyclic chromophore of the anthracycline and the DNA base pairs lying immediately above and below it is the major binding force. This interaction is further stabilized by a variety of ionic and hydrogen bonding interactions (1). The amino sugar appears to lie in the major groove of the DNA helix, with

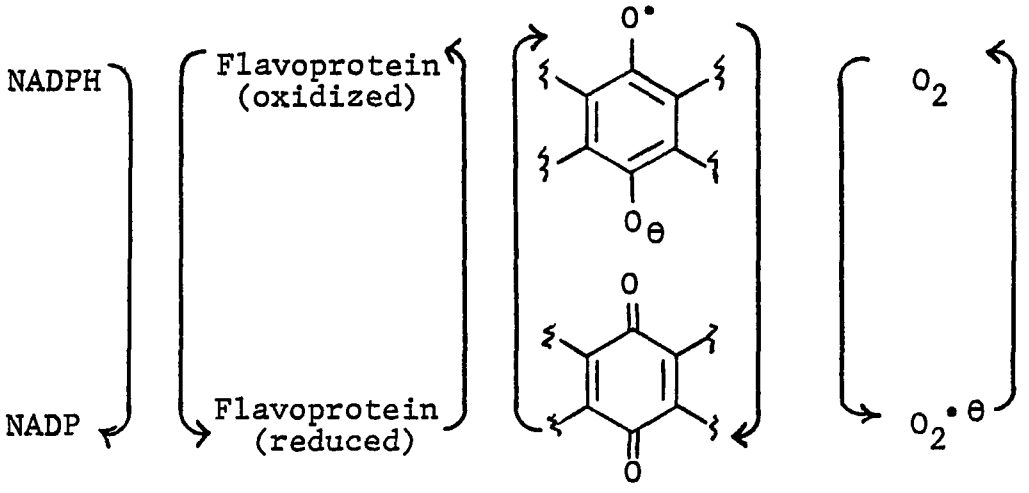
its protonated amino group interacting in an ionic bond with the second phosphate from the intercalation site. Hydrogen bonding between the C-9 hydroxyl and the first phosphate from the site is also possible. Alternatively, an intramolecular C-7 oxygen to C-9 hydroxyl hydrogen bond may exist. In the case of adriamycin, the C-14 hydroxyl may also participate in hydrogen bonding.



Anthracycline A-Ring Conformation

It is thought that the intercalation and binding prevent conformational changes in the DNA helix which are necessary to initiate nucleic acid synthesis, thus causing the death of the cancer cell. However, intercalation can not account for the DNA strand breaks observed in vivo with anthracycline use (23). Recent evidence indicates that the enzyme NADPH cytochrome P-450 reductase, which is present in the microsomes of tumor cells, is capable of catalyzing the single electron reduction of quinone antibiotics (23). In the presence of molecular oxygen this leads to the formation of superoxide radicals, which then would do the actual damage to the DNA strand leading to inhibition of nucleic acid synthesis and

cell death. The tight binding of anthracyclines to DNA would allow formation of superoxide radicals in close proximity to their site of action.



Having a fairly good idea of how anthracyclines produce their effect on cancer cells is very useful in rationalizing differences in activity among the different groups of anthracyclines. Some of the most important structure activity relationships will be outlined and, where possible, related to the proposed model for anthracycline binding to DNA.

Aclacinomycin A and 1-deoxypyrromycin are non-mutagenic in the Ames Salmonella test (24). Daunomycin and adriamycin are highly mutagenic, while N-methyl daunomycin is weakly mutagenic and N-dimethyl daunomycin is non-mutagenic. N-demethyl pyrromycin and N-demethyl aclacinomycin are mutagenic. Aklavinone and daunomycinone are non-mutagenic. This

means that the nature of the amino moiety of the anthracycline glycosides determines mutagenicity. Whether or not the nitrogen is methylated must influence the amino group's interaction with the DNA helix and thus, influence whether the compound is mutagenic.

Comparisons of compounds in the aklavinone and pyrromycin series, in which the only structural difference is the presence or absence of the C-1 hydroxyl group, show that activity, as measured by median survival time of treated versus control animals, is best for the aklavinone series (4). Therefore, compounds not having a C-1 hydroxyl may be better candidates for clinical testing.

Studies involving nogalamycin and C-10 decarbomethoxy nogalamycin indicate that the presence of the ester gives the compound increased potency (25). The potency of marcellomycin and rudolphomycin also decreases when the carbomethoxy group is removed. The C-10 epimers of marcellomycin and rudolphomycin have much reduced potency and slightly reduced activity (4). This structural change would be expected to alter the conformation of the A ring, leading to changes in drug binding characteristics with DNA.

The composition of the saccharide chain also affects the activity of the anthracyclines. Removal of the methyl groups from the 3'-amino group of rhodosamine greatly

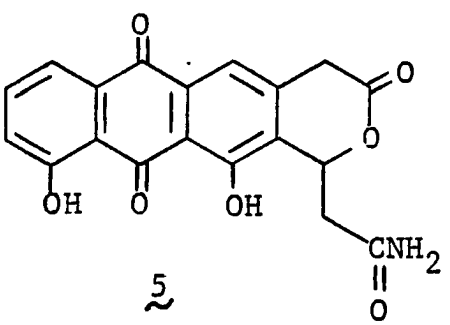
decreases potency, while replacement of rhodosamine by 2-deoxy-L-fucose in aclacinomycin causes complete loss of activity (4).

The length of the saccharide chain plays an important role in determining activity (26). The anthracyclines can be divided into two groups based on their effect on DNA and RNA (ribonucleic acid) synthesis. The first group consists of adriamycin, carminomycin and pyrromycin. These compounds inhibit DNA and whole cell RNA synthesis at nearly equivalent concentrations. The concentrations for inhibiting DNA and nucleolar RNA synthesis are also similar. In the second group, consisting of marcellomycin, mussetamycin and aclacinomycin A, whole cell RNA synthesis is inhibited at six to seven times lower concentrations than for DNA inhibition. Nucleolar RNA synthesis is inhibited at from 170 to 1256 times lower concentrations than for DNA. Because similar aglycones are common to both groups, the difference in the saccharide chain length must cause the difference in activity. It has been suggested that the selective effect on nucleolar RNA synthesis by compounds containing a trisaccharide is due to the long trisaccharide chain occupying the major or minor groove of the DNA helix and interfering with the movement of RNA polymerase along the helix (27).

Many of the comparisons made between the aclacinomycin and adriamycin group compounds point to possible advantages to the use of aclacinomycin A. This prompted human clinical trials of aclacinomycin A to be initiated in Japan in the late 1970's. Preliminary results indicate several advantages to the use of aclacinomycin A (28). A number of side effects are associated with the use of adriamycin, including myelosuppression, stomatitis, alopecia and myocardiopathy (1). Most of these effects are only temporary or can be easily treated, but the cardiotoxicity is a serious problem. It takes the form of temporary EKG changes and irreversible dose-related deterioration of the heart muscle, which is a potential cause of conjestive heart failure. If total cumulative doses are kept below 550 mg/m^2 (29), the cardiotoxicity is not a major problem. No good mechanism has been suggested for anthracycline cardiotoxicity. Adriamycin is known to cause degeneration of mitochondria in cardiac cells and this may play an important role in the toxicity (30). Clinical evidence to date gives no indication of permanent heart damage related to aclacinomycin A use, and the other toxic side effects appear to be milder or less frequent than when adriamycin is used (28). Another important advantage of aclacinomycin is that it is active when given orally, while adriamycin and daunomycin are not (4).

It has been found recently that combinations of anti-cancer drugs often work better than the administration of one drug alone. For example, adriamycin is often given in combination with vincristine, allowing the same anti-tumor effect to be realized from a smaller dose of the toxic anthracycline. Studies in animal systems using P388 leukemia show that aclacinomycin, in combination with cyclophosphamide or vincristine, causes a synergistic therapeutic effect in producing significant lengthening of life span, while none of the drugs alone produced the same effect (31).

One last example of another recently discovered compound is ekatetrone 5. While ekatetrone is not formally considered an anthracycline, it has many structural features in common with the 11-deoxyanthracyclines.

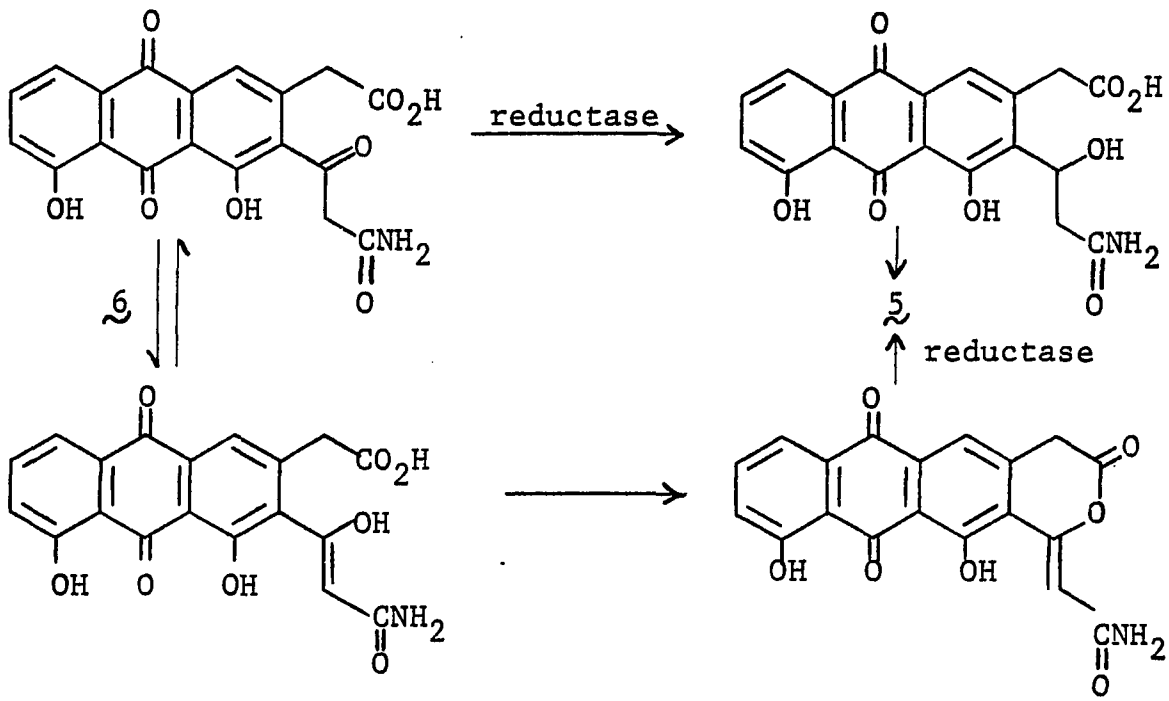


5

Ekatetrone was isolated from a strain of Streptomyces aureofaciens and its structure was determined by chemical and spectral means (32). It has no antibacterial activity,

but in vivo testing showed that it inhibits the growth of Ehrlich ascites carcinoma (32). No comparisons of activity with any anthracyclines have been reported.

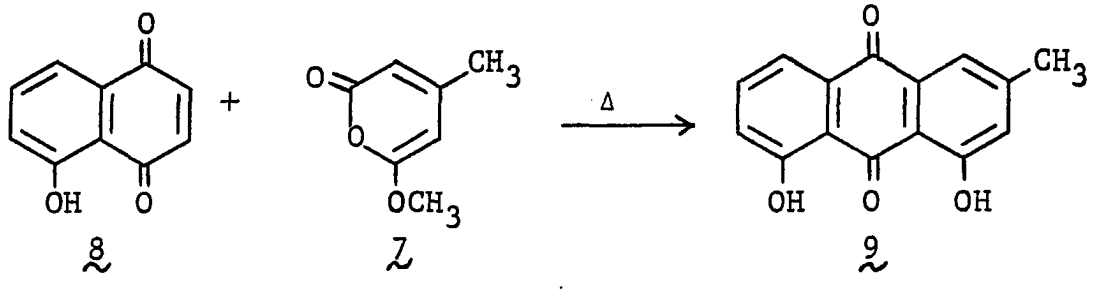
Ekatetrone is thought to arise biosynthetically from protetrone 6, a known metabolite of Streptomyces aureofaciens (5). A biosynthetic relationship has also been proposed between protetrone and the tetracyclines (33).



Because of the clinical importance of adriamycin and daunomycin and the need to find analogues with fewer side effects, a great deal of research has been done by synthetic chemists to find efficient methods of making these compounds, especially the aglycone portion of the molecule. Methods published through early 1979 have been reviewed (34). More

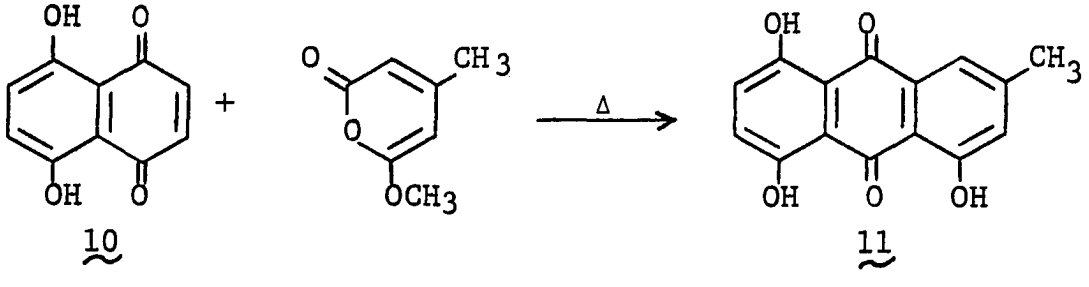
recent methods are referenced in a paper by Kelly and coworkers (35).

As investigators have become aware of the possible advantages of clinical use of aclacinomycin A, methods have been developed for the synthesis of 11-deoxyanthracyclines. Jung and Lowe (36) hoped to use a Diels-Alder approach for synthesizing aklavinone and pyrromycinone. Model studies showed that the pyrone 7 reacted in a regiospecific manner with juglone 8 to give, after oxidation and demethylation, chrysophanol 9 in 62% overall yield. None of the other

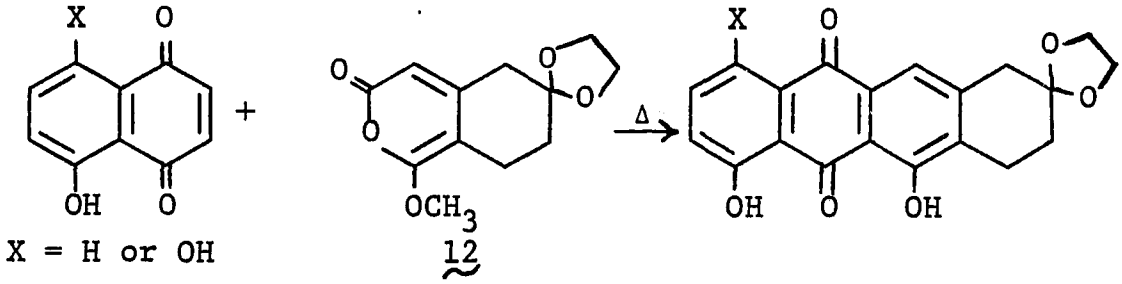


8 7 9

regioisomer was isolated. The pyrone also reacted with napthazarin 10 in a similar manner to give helminthosporin 11 in 38% overall yield. Jung planned to use the reaction of bicyclic pyrone 12 to build up the tetracyclic skeleton.



10 11



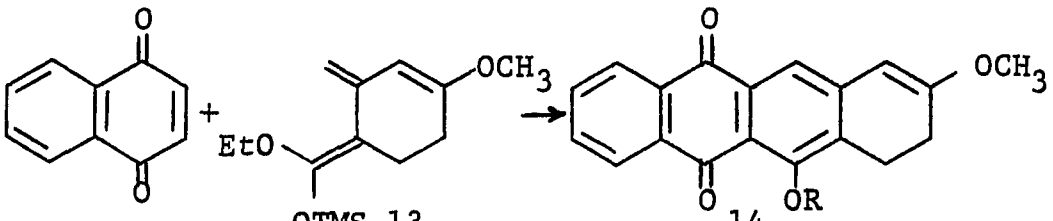
X = H or OH

12

No further progress has been reported on this route since the initial report in early 1978. Pyrone 12 may not have been obtainable. While Jung and Lowe had a nice solution to the problem of regiospecific introduction of the oxygenated functionality, even if the desired tetracyclic compound had been obtained, there may have been formidable problems associated with further regiospecific functionalization of the A ring.

Jung and Lowe's work points out the importance of developing regiocontrolled methods for generating the DCB rings. The 11-deoxyanthracyclines lack the symmetry in rings C and B found in the adriamycin series, which somewhat simplifies the synthesis of adriamycin.

Very recently another regiospecific Diels-Alder approach has been published (37). Diels-Alder reaction of diene 13 with various quinones at room temperature gave several tetracyclic compounds. Addition to juglone 8 is regiospecific and formation of compound 16 constitutes a formal synthesis of recently isolated 11-deoxydaunomycinone.

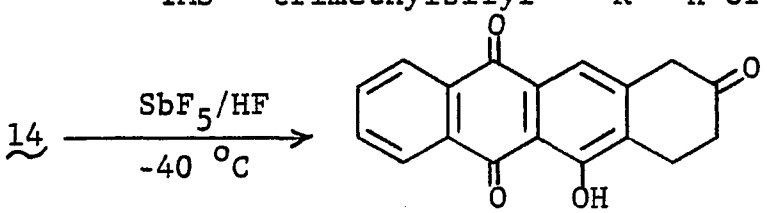


13

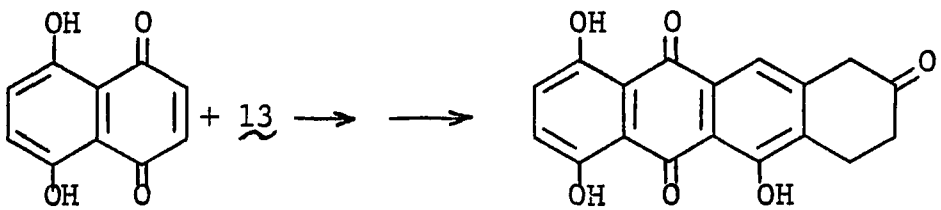
TMS = trimethylsilyl

14

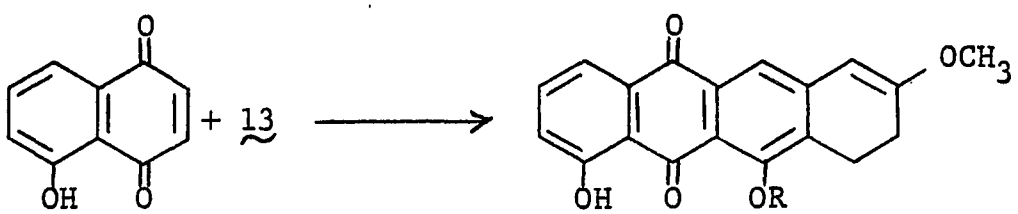
R = H or Et (1:4)



67% overall yield

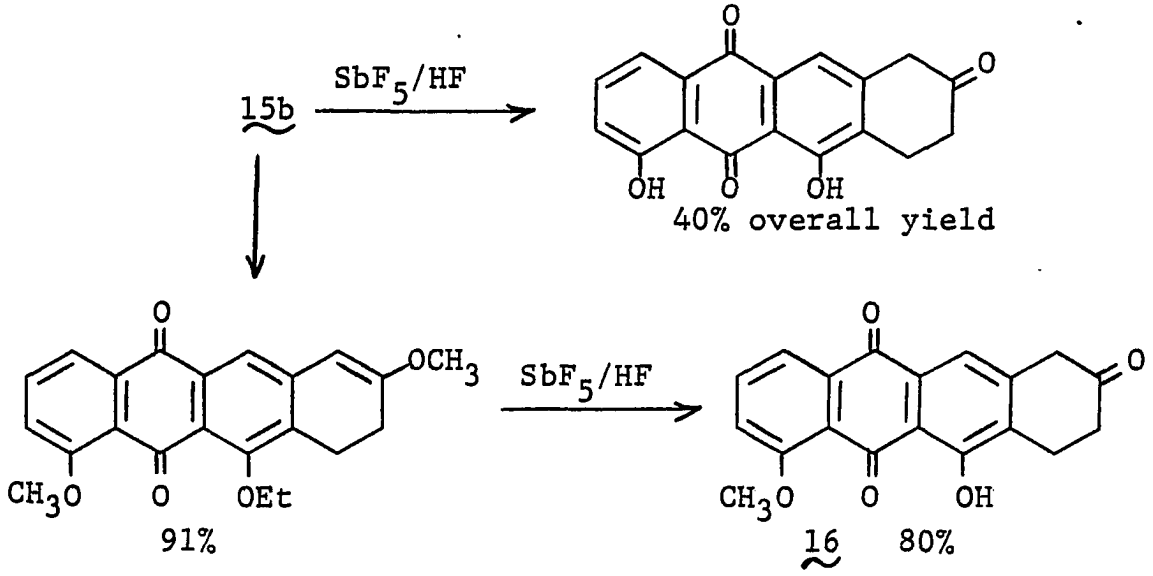


50% overall yield



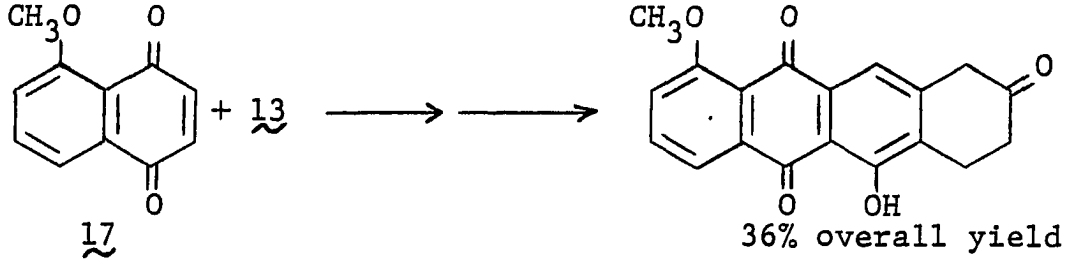
15a R = H 18%

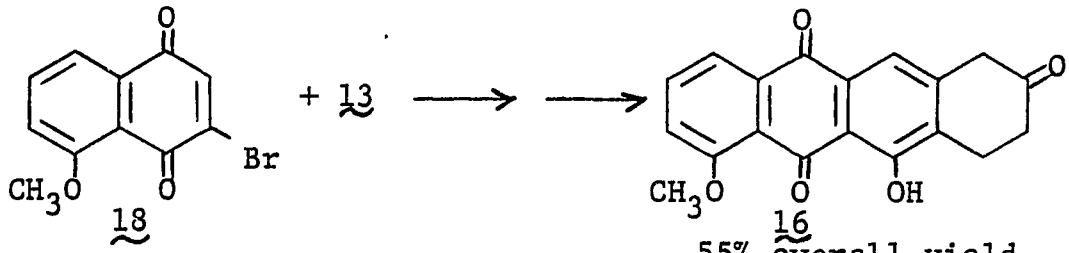
15b R = Et 43%



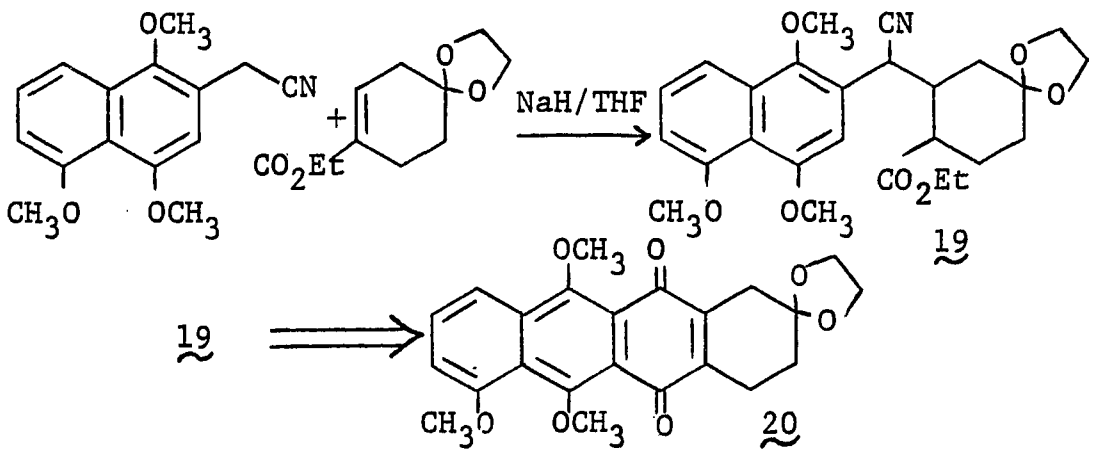
Further elaboration of the A ring from this type of ketone has been accomplished in the adriamycinone and daunomycinone series (38).

The reaction product of diene 13 with juglone methyl ether 17 has the opposite regiochemistry of the product with juglone. The known regiochemistry of addition of vinyl ketene acetals to haloquinones (39) was also observed with quinone 18 and diene 13. This method provides an extremely efficient route to 11-deoxydaunomycin and 11-deoxyadriamycin.



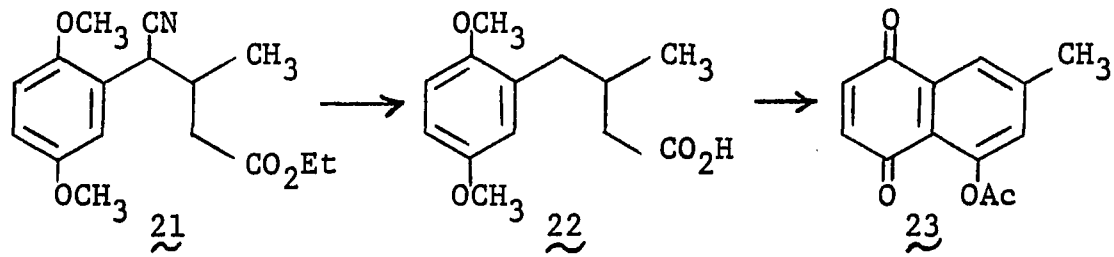


The use of carbanion chemistry has provided another method for synthesizing anthracyclines. Parker and Kallmerten (40) and Kende and coworkers (41) have independently reported the use of the anion of substituted benzyl nitriles to generate the daunomycinone skeleton 20.

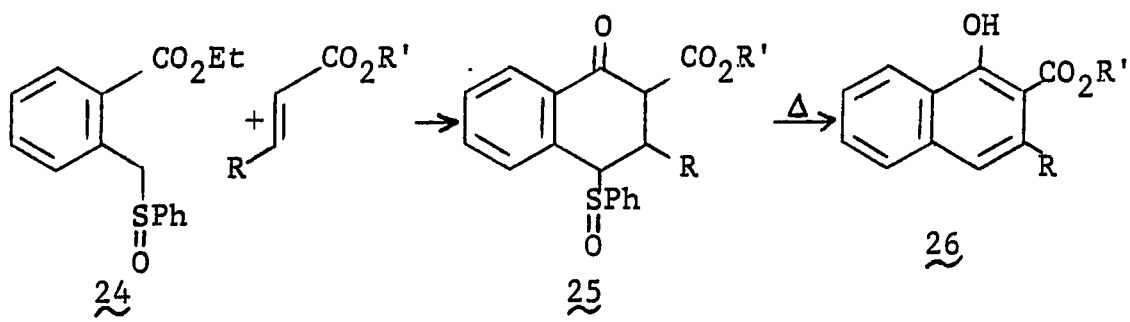


At the most recent American Chemical Society meeting, extensions of this work to the 11-deoxyanthracyclines were reported (42). In a model system, Parker and Kallmerten hydrolyzed the Michael adduct 21 to the acid and then subjected the acid to Birch reduction conditions, causing decyanation to 22. After Friedel-Crafts ring closure, oxidation and acetylation, a model 23 for the BC rings of

11-deoxyanthracyclines was obtained. This should provide a completely regiospecific route to 11-deoxydaunomycinone.

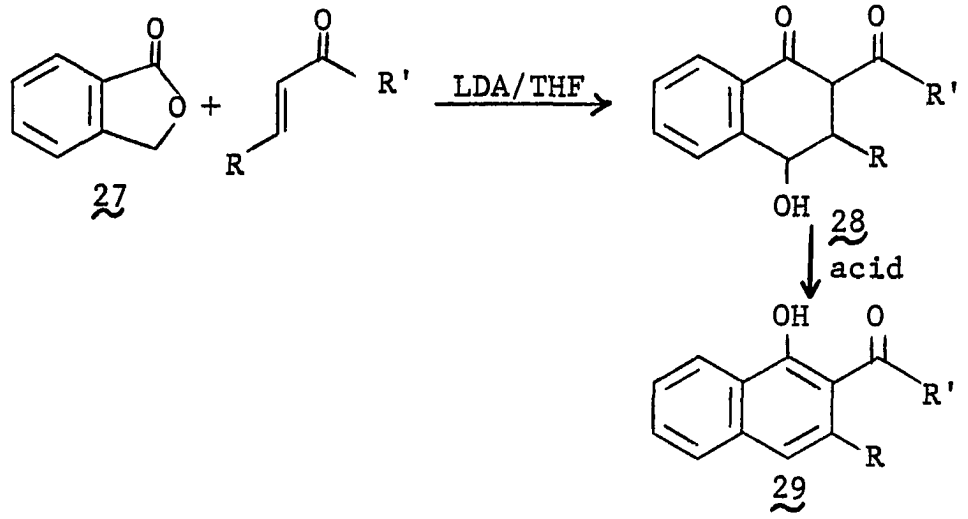


In the last few years, several other annelation methods based on carbanion chemistry have been developed which have potential for application to anthracycline synthesis. Hauser and Rhee (43) reported that certain benzylic sulfoxides 24 undergo Michael addition and subsequent annelation with unsaturated esters to give bicyclic products 25. Thermal elimination produces phenols 26.



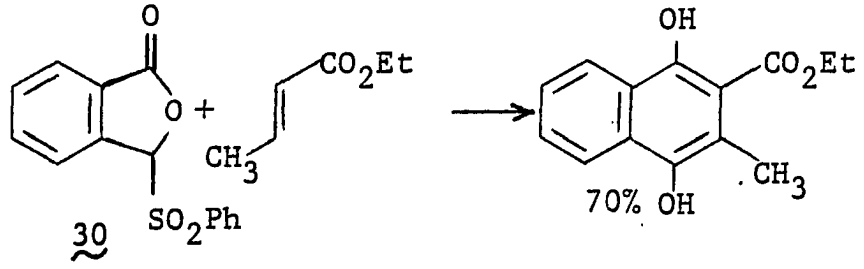
Methods which use the anion of variously substituted phthalides have proven to be very useful. Broom and Sammes (44) first reported that the anion of phthalide 27 can be formed with LDA (lithium diisopropyl amide) and, in a one

pot annelation reaction with unsaturated carbonyl compounds, produce keto-alcohols 28 in moderate yield. When treated with acid, the keto-alcohols gave phenols 29.



27 29

Further application of phthalide anions was developed at the same time by Kraus and Sugimoto (45) and Hauser and Rhee (43). Using substituted phthalide anions in the annelation process, hydroquinones can be obtained directly. Hauser and Rhee used sulfone substituted phthalides 30, while Kraus and Sugimoto used cyano substituted phthalides 31. Both processes give hydroquinones in good yield.



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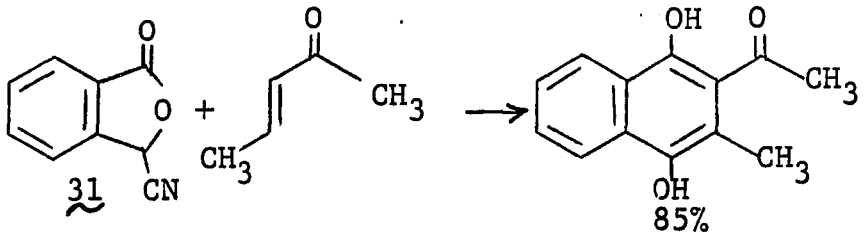
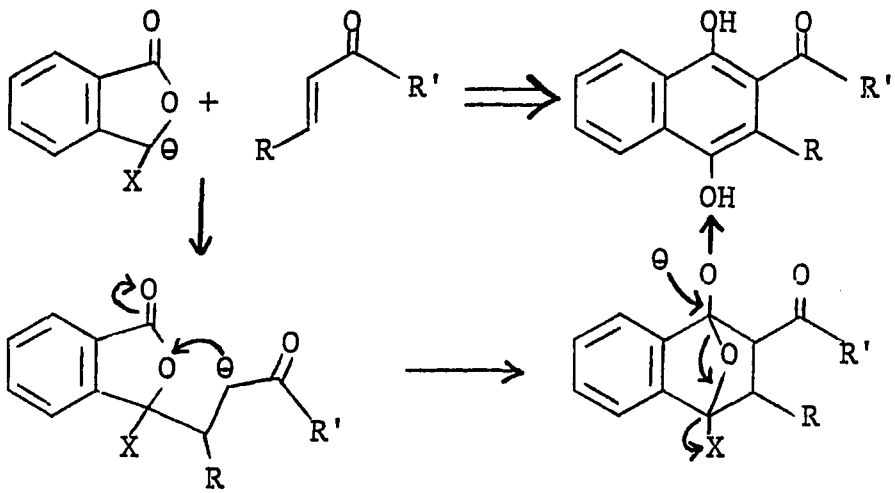


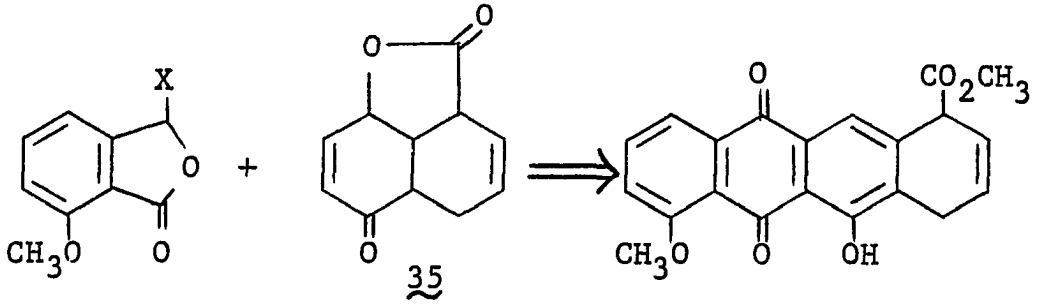
The mechanism proposed for this process is shown below.

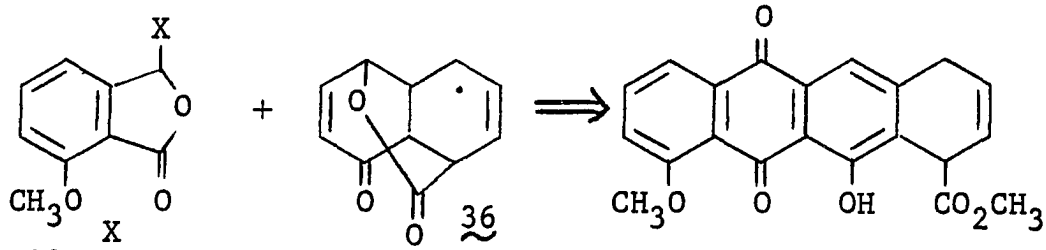


The substituent X must serve both as a good carbanion stabilizing group and as a good leaving group. The sulfone and cyano groups fit both criteria well. The use of the simple thiophenyl substituted phthalide for annelations will be detailed in the next section.

The ability of these phthalides to undergo annelation reactions was utilized by a group at Syntex Research in an approach to the synthesis of aklavinone (46). They attempted using all three phthalides 32-34 to add to the unsaturated ketones 35 and 36. They found that only the cyano

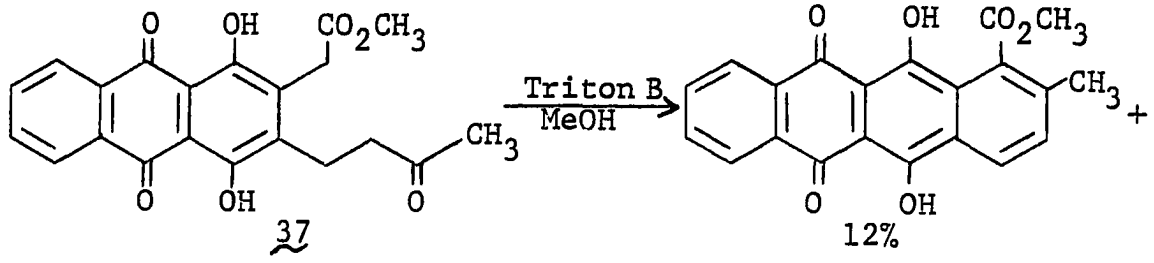
substituted phthalide 33 underwent the desired reaction, giving the annelation product in 30% yield (47). These tetracyclic compounds may be difficult to properly functionalize to give aklavinone.

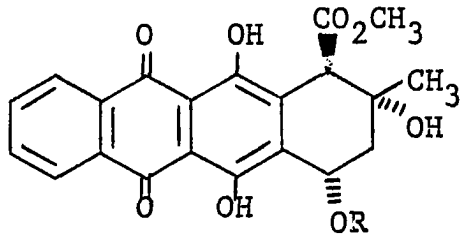




	X
32	SO_2Ph
33	CN
34	SPh

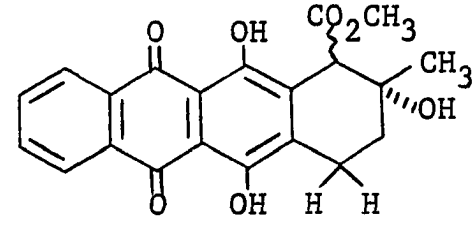
Finally, a model study for the synthesis of the A ring portion of aklavinone has been reported (48). Reaction of ketoester 37 with Triton B (benzyltrimethylammonium methoxide) in methanol yielded a mixture of products. The ratios of products were different if the hydroxide form of Triton B was used or if the reaction time was varied.





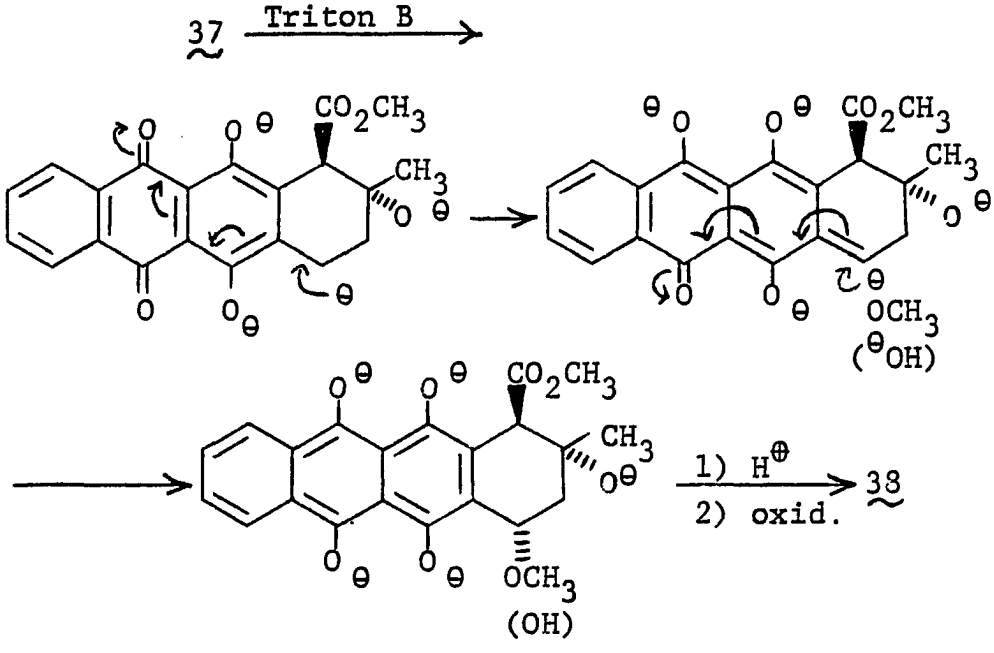
38 R = H 21%
R = CH_3 24%

+



11%

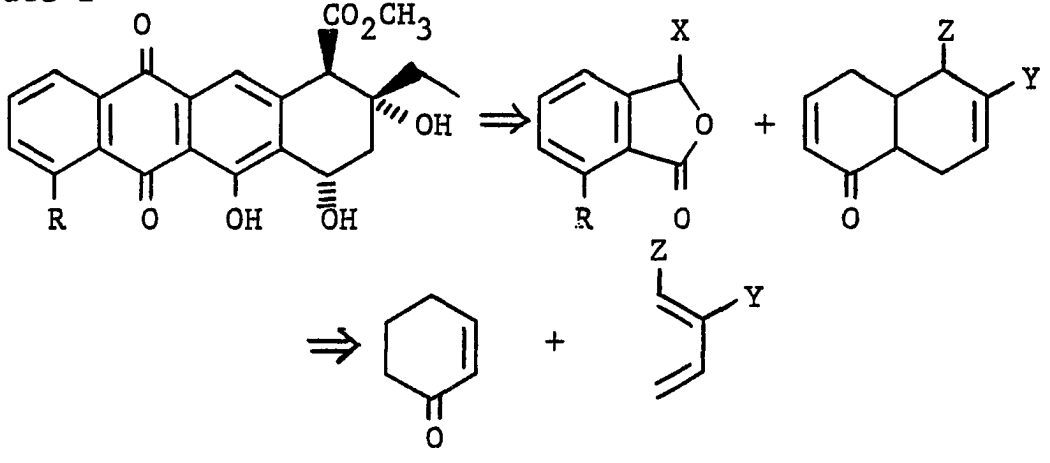
The following mechanism was proposed for formation of products 38.



RESULTS AND DISCUSSION

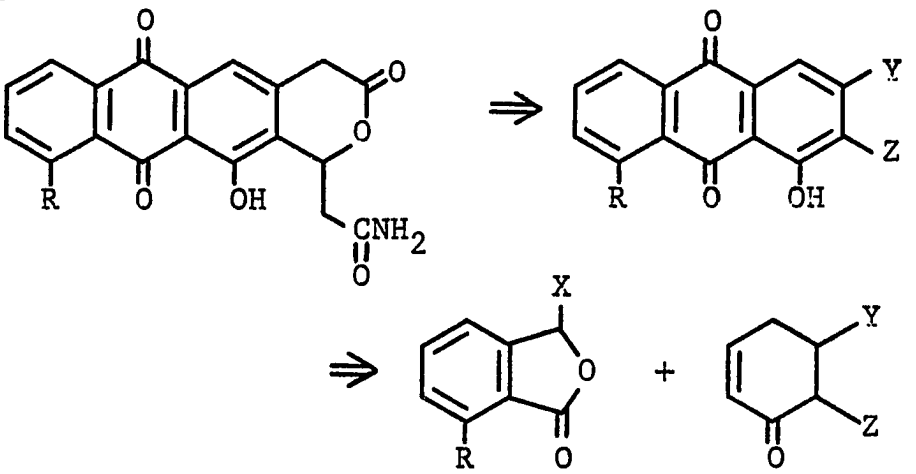
Previous work from our laboratory (45) had demonstrated the utility of phthalide annelations for the rapid and efficient synthesis of quinones. We hoped to use this reaction as the basis for synthesizing aklavinone and ekatetrone. Retrosynthetic analysis indicated two possible routes to these molecules starting from a suitable B ring precursor. The first route utilized a Diels-Alder reaction to introduce the A ring of aklavinone. A phthalide annelation

Route 1

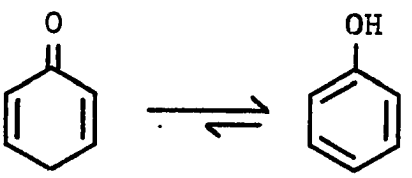


would then be used to introduce the CD rings of the tetracyclic system. The second route, which would be better suited for synthesizing ekatetrone, began with a phthalide annelation to a functionalized cyclohexenone. The functionality on the enone would then be used in the final steps to form the A ring.

Route 2



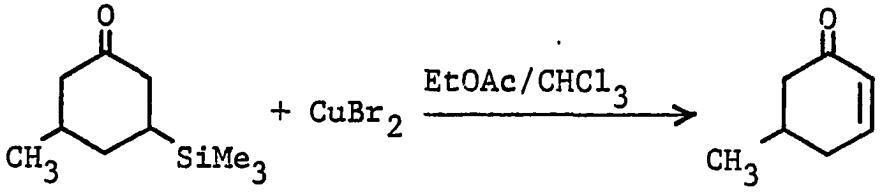
Studies were undertaken to determine the feasibility of using the first route for synthesizing aklavinone. An ideal B ring precursor might be 2,5-cyclohexadienone (39). After the initial Diels-Alder reaction, the enone portion of



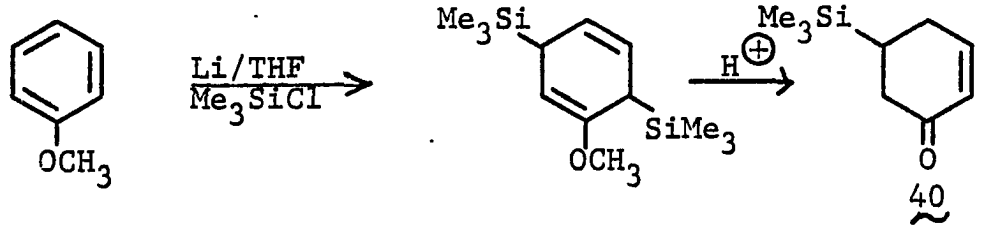
39

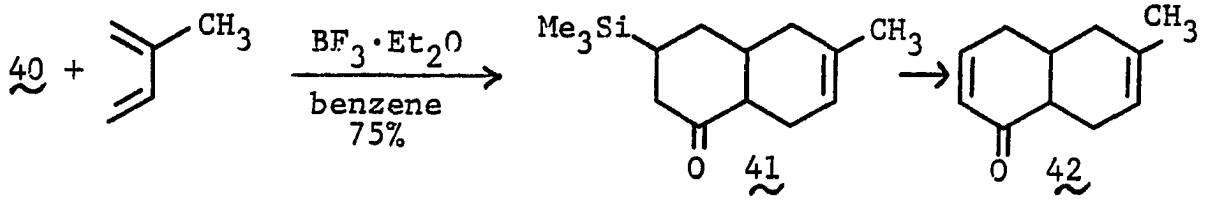
the AB ring system would be used in the phthalide annelation. Although 2,5-cyclohexadienone has been isolated and characterized at -196 °C (49), it unfortunately exists in an unfavorable equilibrium with phenol at normal temperatures. If 39 was available, it would probably give some Diels-Alder product resulting from the addition of two molecules of the diene, as is often the case with benzoquinone.

Because of these difficulties, we sought an equivalent of 39 in which one of the double bonds was protected with a functional group that could easily be eliminated. Since Ager and Fleming (50) had reported the transformation of β-silyl ketones to enones in good yield, enone 40 might be a desirable B ring precursor. We were happy to discover



that 40 had been reported in the literature (51). Compound 40 could be readily synthesized from anisole in large quantities.

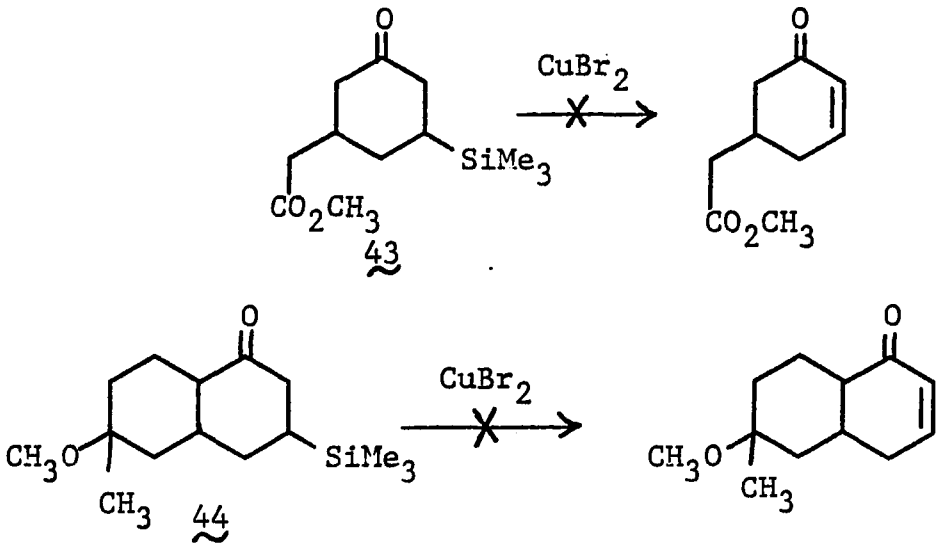




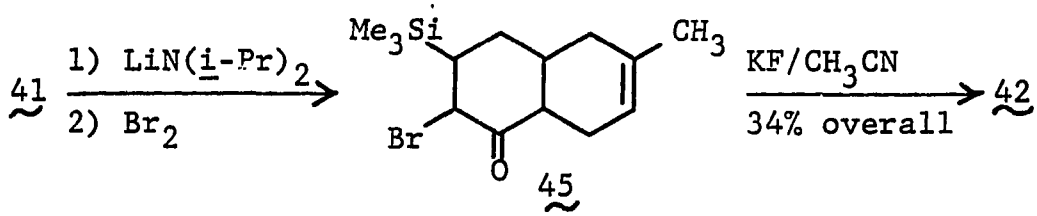
The Lewis acid catalyzed reaction of 40 with isoprene gave 41 in good yield. Attempts to use the Ager and Fleming conditions to form the desired bicyclic enone 42 were

unsuccessful. While the product of the reaction contained no silyl group, the trisubstituted olefin was also gone. A by-product of the reaction, HBr, may have been adding to the olefin. When the reaction was run in the presence of excess base, however, none of the desired enone 42 was isolated. Examples were also found in the literature wherein $CuBr_2$ was used for the bromination of olefins (52).

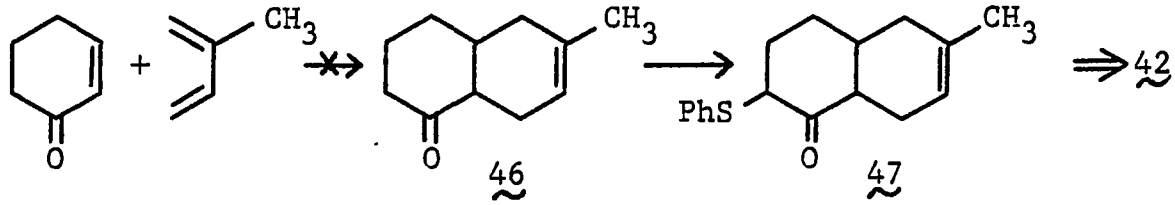
Examination of the reactions of compounds such as 43 and 44 indicated that the Ager and Fleming reaction was not at all general. Saturated hydrocarbon functional groups seem to be the only functional groups compatible with the reaction conditions.

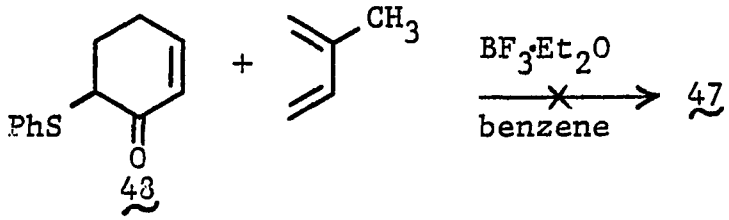


The bromoketone 45 was synthesized and treated with KF in CH_3CN to give 42 in poor yield. The yield was not high enough for the reaction to be considered useful as the first



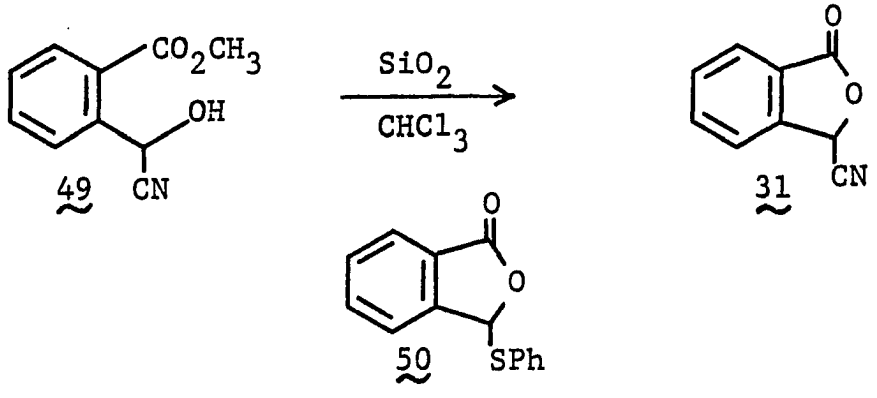
part of a multi-step synthetic sequence. Alternative syntheses of 42 were examined. While cyclohexenone is reported to react with butadiene in good yield (53), none of the desired product 46 was obtained on reaction of cyclohexenone with isoprene. The reaction of isoprene with 48 gave dimerized isoprene and the original enone as products.





The difficulties associated with synthesizing the bicyclic AB units needed for the first synthetic route led to an examination of the use of the second route for synthesizing both aklavinone and ekatetrone. While cyano

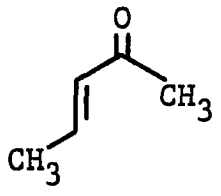
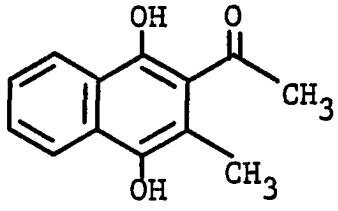
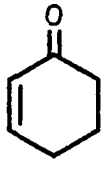
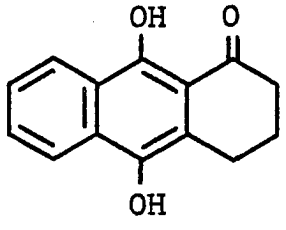
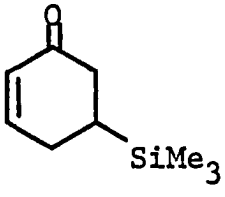
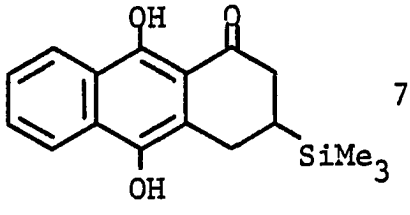
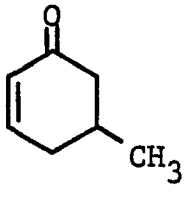
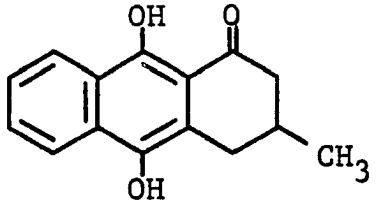
phthalide 31 had worked well in annelation reactions (45), it was difficult to synthesize in quantities large enough to use in a multi-step synthesis. We found that on a reasonably large scale cyanohydrin 49 could be converted to cyano phthalide 31. However, the product contained unidentifiable impurities which could not be removed by recrystallization or column chromatography. The use of catalysts such as trifluoroacetic acid and p-toluenesulfonic acid for the lactonization did not provide 31.



49 31 50

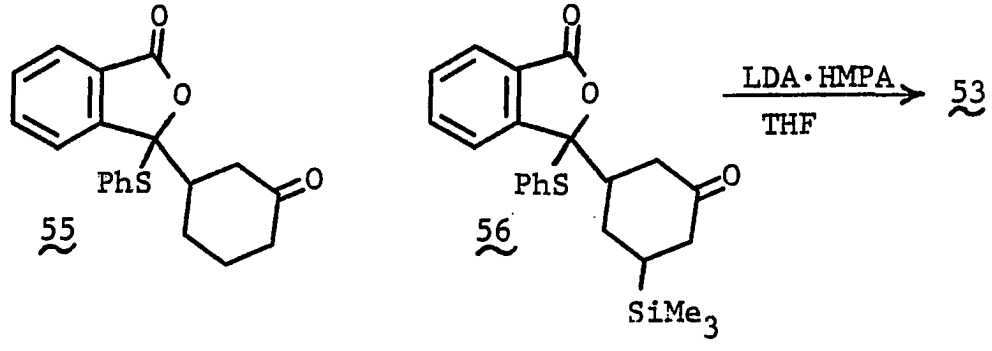
The thiophenyl phthalide 50 was easier to make in large quantities and its ability to undergo the annelation reaction was examined. Under the reaction conditions used for cyano phthalide annelation ($LiN(i\text{-}Pr)_2$/THF/-78 °C), only Michael addition products were isolated (54). We examined the effect on the reaction of varying the reaction conditions. It was found that optimum yields of annelation products could be obtained by using two equivalents of hexamethylphosphoramide (HMPA), 1.5 equivalents of $LiN(i\text{-}Pr)_2$ (LDA) and allowing the

reaction mixture to stir for 72 hours at 0 °C. Some examples of products obtained from thiophenyl phthalide annelations are shown below.

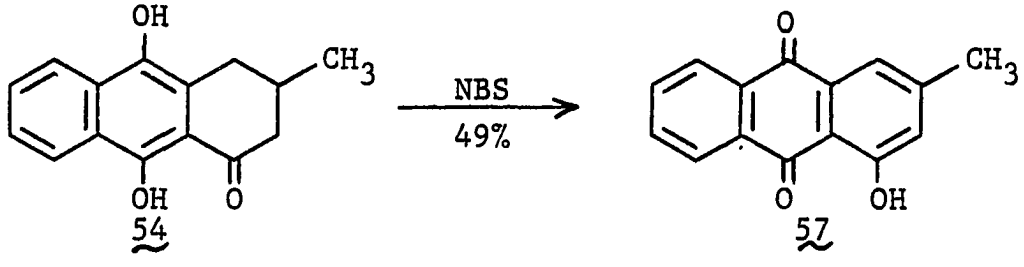
Unsaturated carbonyl compound		Annelation product	
	51		30%
	52		38%
	53		70%
	54		66%

The proposed annelation mechanism involves an initial Michael addition of the phthalide anion to the unsaturated carbonyl compound. If the Michael adducts are very polar, they precipitate out of solution giving a low yield of annelation product. The annelation reaction with

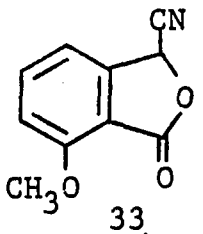
cyclohexenone yielded 32% of the Michael adduct 55. The annelation reaction with 5-trimethylsilyl cyclohexenone yielded 5-10% of Michael adduct 56. Treatment of 56 under the annelation conditions provided 53.



It was found that 54 could be oxidized in one step to pachybasin (57), a naturally occurring fungal metabolite (55). Treatment of 54 with N-bromosuccinimide (NBS) resulted in benzylic bromination and subsequent loss of HBr to give a tricyclic phenol. When exposed to air, the hydroquinone was oxidized to the quinone. This provided a very efficient two step synthesis of pachybasin in an overall yield of 32%.

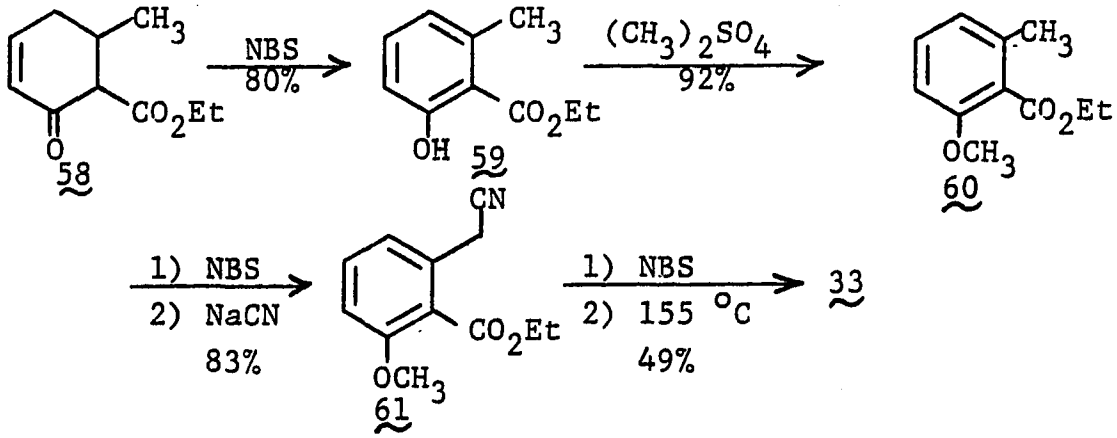


Studies have shown that 4-demethoxydaunomycin is more active than daunomycin (56). Elaboration of tricyclic compounds 53 or 54 to tetracyclic systems would give 4-deoxyaklavinone and 4-deoxyekatetrone. It would be interesting to compare the activity of these deoxy compounds to the naturally occurring substances. For a total synthesis of aklavinone and ekatetrone a method was needed for introducing the oxygen functionality in the D ring. We felt that phthalide 33 would allow regiospecific introduction of the C-4 oxygen.



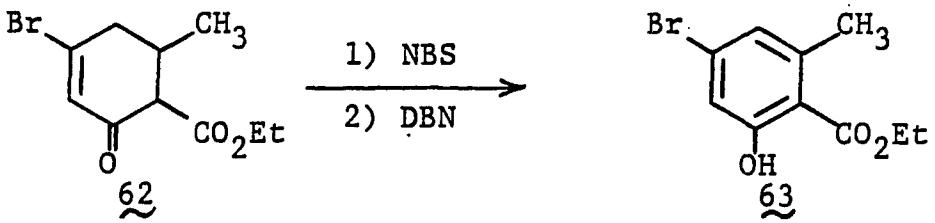
33

The synthesis of 33 was a major challenge. No commercially available aromatic starting material could be obtained which would allow elaboration to 33. After much experimentation, a six step synthesis was developed starting with readily available enone 58 (57). The initial aromatization (58 → 59) worked quite well, with the allylic bromination and loss of HBr occurring in one pot. This appears to be a good method of aromatizing cyclohexenones. Treatment of cyclohexenones with $CuBr_2$ in CH_3CN is also reported to

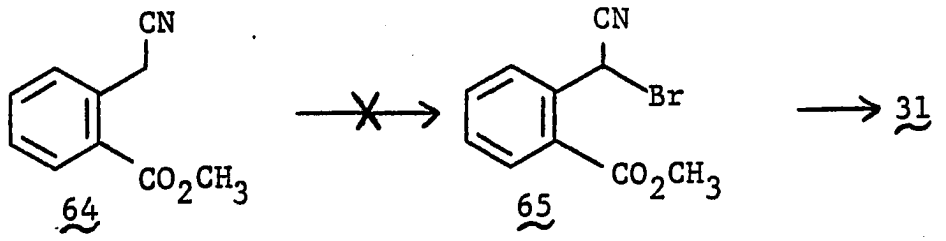


give phenols (58). In this case, reaction of 58 with $CuBr_2$ gave 59 in 60% yield.

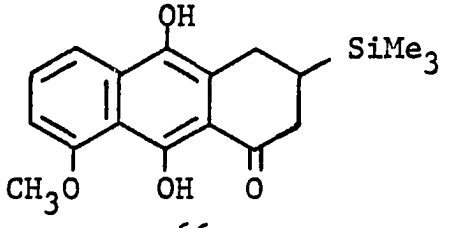
Enone 62 could be aromatized to phenol 63 in 63% overall yield. However, the allylic bromide would only aromatize after treatment with 1,5-diazabicyclo[4.3.0]non-5-ene (DBN).



Transformation of 61 to 33 involved formation of the α-bromonitrile, followed by thermal elimination (155 °C/10 mm) of ethyl bromide to yield the lactone (59). An attempt was made to use this thermal elimination to synthesize the unsubstituted cyano phthalide 31, but surprisingly, bromonitrile 65 could not be obtained.



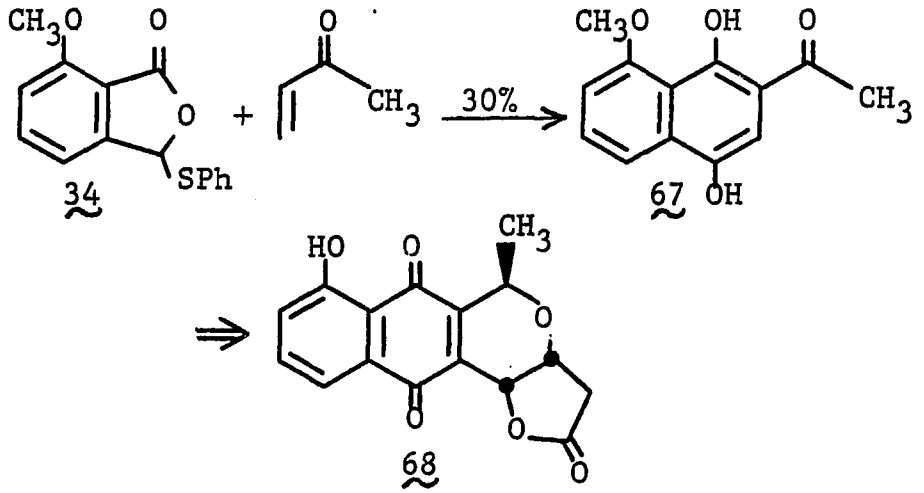
Having obtained phthalide 33, it was subjected to the annelation reaction conditions used for thiophenyl phthalide 50. The results were quite disappointing. While the initial Michael addition appeared to take place, little or no annelation product could be isolated. When 33 was reacted with 40, a complex product mixture was obtained. About a 40% yield of annelation product 66 was isolated.



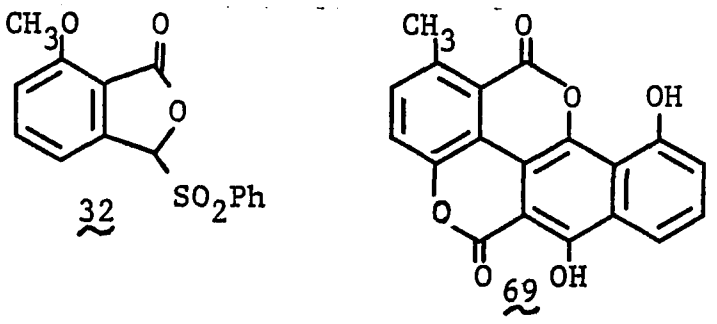
66

Hydroquinone 66 could not be obtained in completely pure form, but its structure was assigned on the basis of nuclear magnetic resonance (NMR) and infrared data.

The use of phthalide 34 (60) gave no annelation products with 5-methyl cyclohexenone or 5-trimethylsilyl cyclohexenone. Phthalide 34 has been used to prepare hydroquinone 67, a key intermediate in a regiospecific synthesis of kalafungin 68 (61). Again, the yield of annelation product



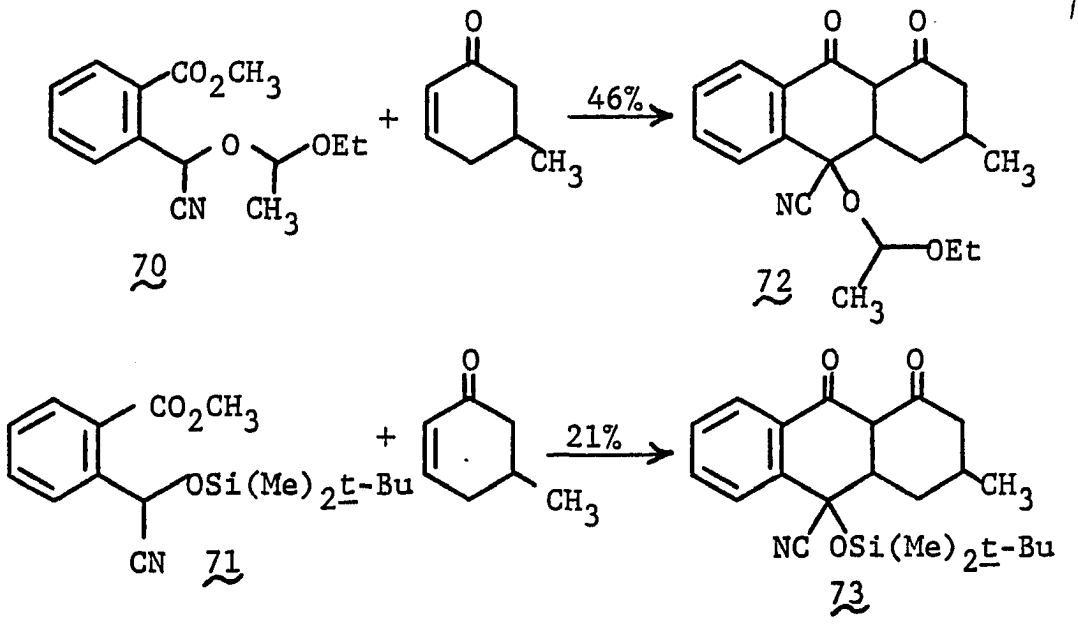
was quite low. Hauser and Combs used the phthalide 32 in a regiospecific synthesis of chartreusin aglycone 69 (62). The phthalide 32 also did not afford high yields of annelation products.



We felt that there were two possible reasons for the poor annelation results with 33. Firstly, a certain amount of strain may be involved in forming the tricyclic tetrahedral intermediate leading to the hydroquinone. Secondly, the methoxyl group is an electron donating group and may

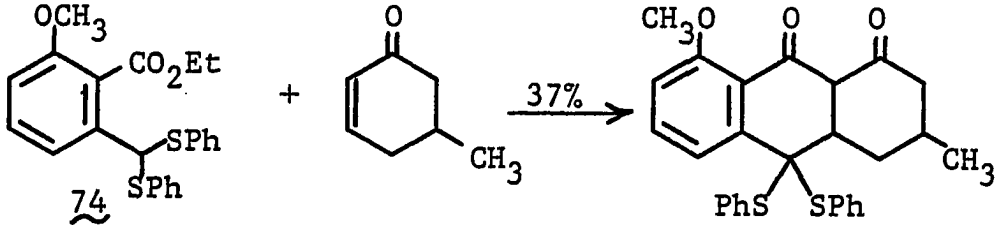
decrease the electrophilicity of the lactone carbonyl. To examine the first problem, the protected cyanohydrins 70 and 71 were prepared.

Protected cyanohydrins are known to undergo Michael addition to unsaturated ketones (63) but no reactions of the anions of protected cyanohydrins containing an ortho carbonyl group have been reported. The compounds 70 and 71 were reacted with 5-methyl cyclohexenone under the standard annelation conditions. Compound 71 gave a low yield of 73.

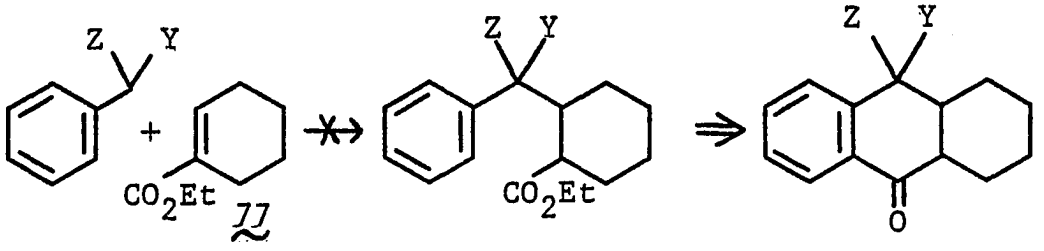


This was due to the instability of the silyl protecting group under the reaction conditions. Compound 70, which was more stable to the reaction conditions, gave a fair yield of 72. Some thioacetals are also known to add to unsaturated carbonyl compounds (64). The reaction between 74 and

5-methyl cyclohexenone gave a 37% yield of annelation product 75.



A similar reaction sequence was attempted by Parker and Kallmerten (65). They were unable to obtain Michael addition products from the reaction of 76a and 76b with 77.

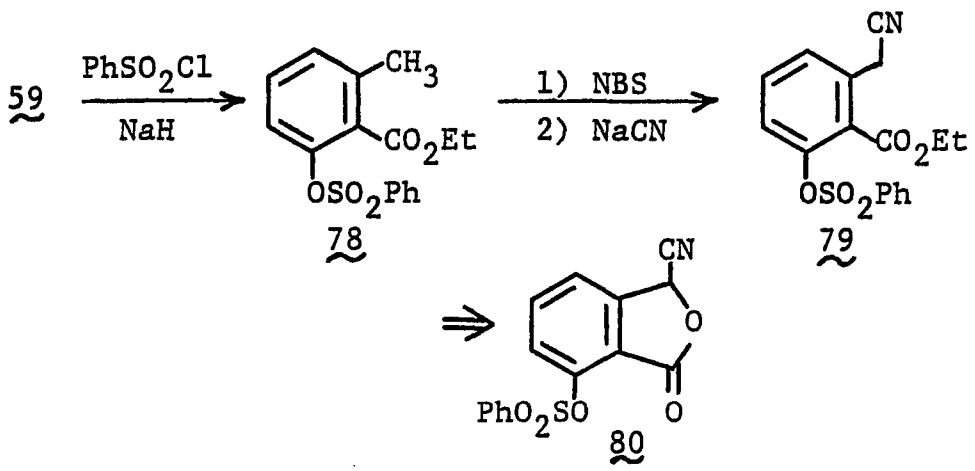


76a Z = Y = $SCH_2CH_2CH_2S$

76b Z = CN Y = $OCH(CH_3)OEt$

Our results seemed to indicate that strain is not the major problem, since the annelations involving the protected cyanohydrins and thioacetal gave lower yields of product with 5-methyl cyclohexenone than did phthalide 50. The electron donating effect of the methoxyl group is probably the major factor interfering with the annelation process. An attempt was made to synthesize phthalide 80 from 59.

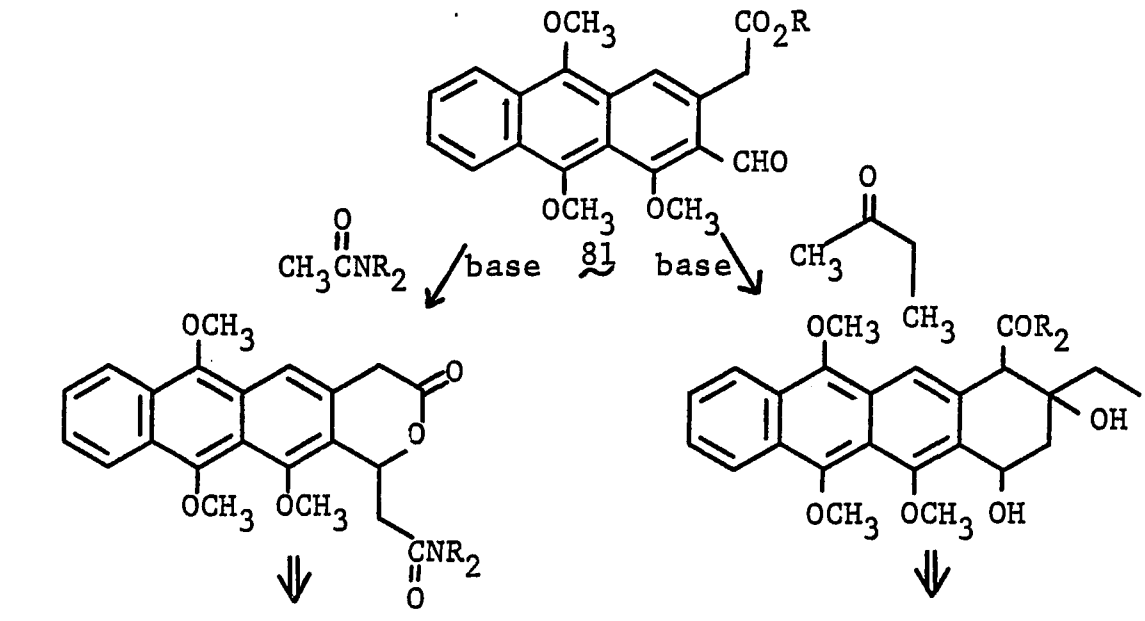
The electron withdrawing phenylsulfonyloxy group would be expected to maintain or increase the electrophilicity of the lactone carbonyl. Transformation of 78 to 79 occurred

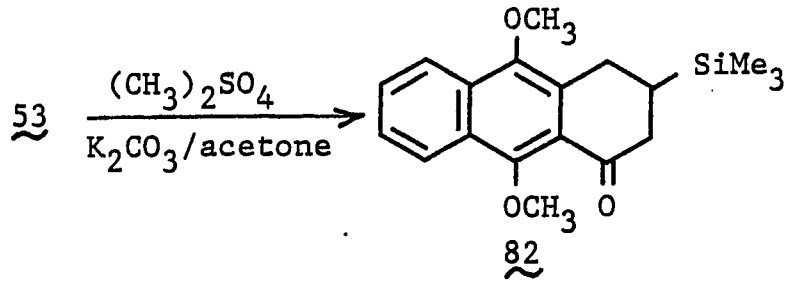


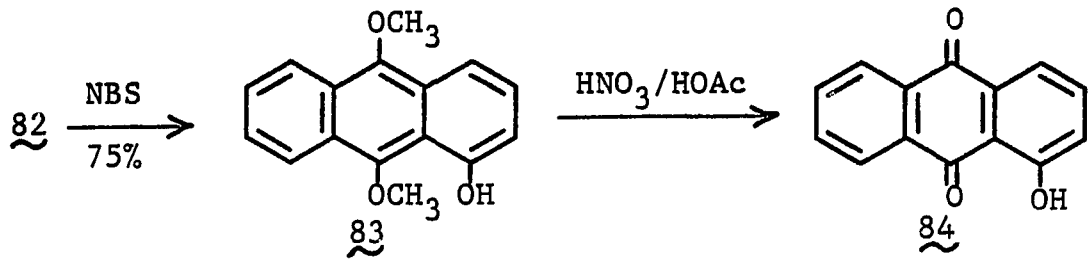
in 12% overall yield. Both steps produced significant amounts of unidentifiable side products. Because of the low overall yield, no effort was made to transform 79 into 80.

The elaboration of a tricyclic hydroquinone to deoxyaklavinone and deoxyekatetrone was our next goal. We felt that compound 81 would be a key intermediate for both syntheses.

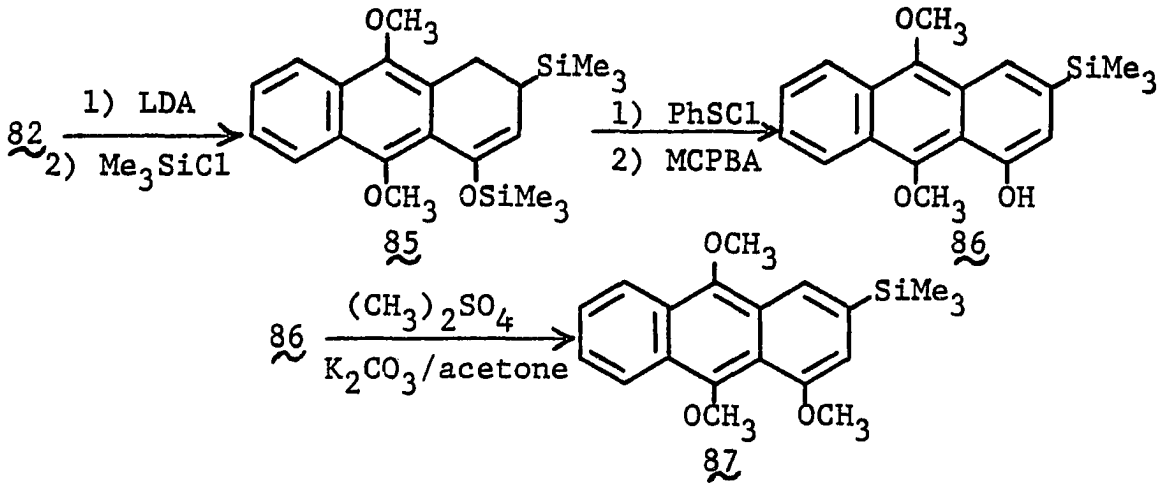
We decided to use the known reactivity of aryl silanes in an effort to synthesize 81. Hydroquinone 53 could be protected as its dimethyl ether 82 in excellent yield. Benzylic bromination gave aromatized product 83. The loss of the silyl group was not unexpected. Phenol 83 could be


OCH3
CO2R
CHO
OCH3
OCH3
81
CH3CNR2
O
base
base
CH3
OCH3
CH3
COR2
OH
OCH3
OCH3
OH
CNR2
O
4-deoxyekatetrone
4-deoxyaklavinone


53
(CH3)2SO4
K2CO3/acetone
OCH3
SiMe3
OCH3
O
82

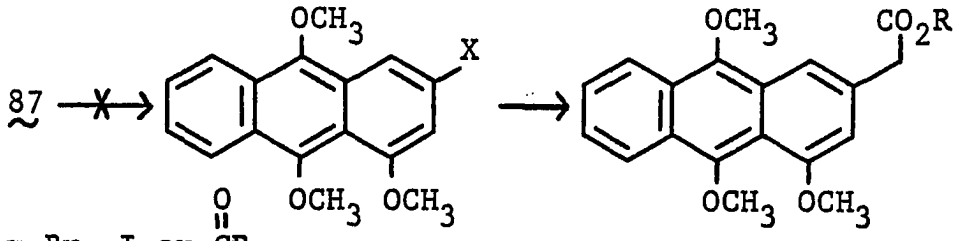

82
NBS
75%
OCH3
OCH3
OH
83
HNO3/HOAc
O
O
OH
84

oxidized to the known quinone 84. To obtain the desired silyl phenol, transformations which would not generate a cation beta to the silyl group had to be used. Enol silyl ether 85 could be prepared in quantitative yield. It was transformed into an α-thiophenyl ketone and oxidized with m-chloroperoxybenzoic acid (MCPBA) to the sulfoxide without isolation of the thiophenyl ketone. The sulfoxide elimination occurred in situ between 0 °C and room temperature to give phenol 86 in an overall yield of 57%. Generally, sulfoxide eliminations take place at temperatures near 100 °C.



Aryl silanes are known to undergo a number of electrophilic substitution reactions at the carbon bearing the silicon (66, 67a). We hoped to replace the trimethylsilyl group of 87 with either a halogen or an acyl group. The halogen or acyl group would then be transformed into the

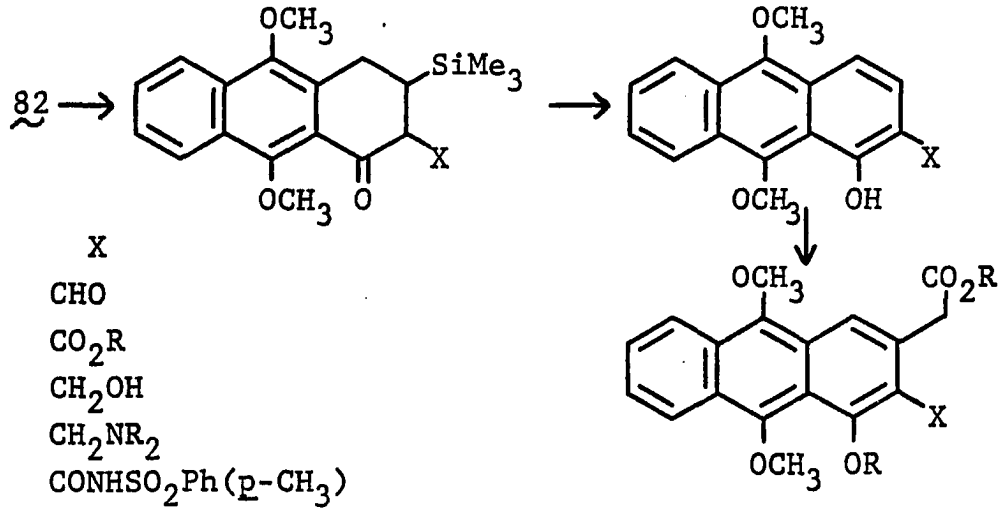
acetic acid ester side chain of key intermediate 81. Reactions of 87 were performed with Br_2 (67b), I_2 (67c) and ICl (67d). In every case, either starting material was recovered or halogenation appeared to occur at other positions on the aromatic system. Friedel-Crafts acylation with acetyl chloride (66) was also attempted, but only starting material was recovered. Apparently, carbons other than the one bearing the silicon are more activated toward substitution.



X = Br, I or CR

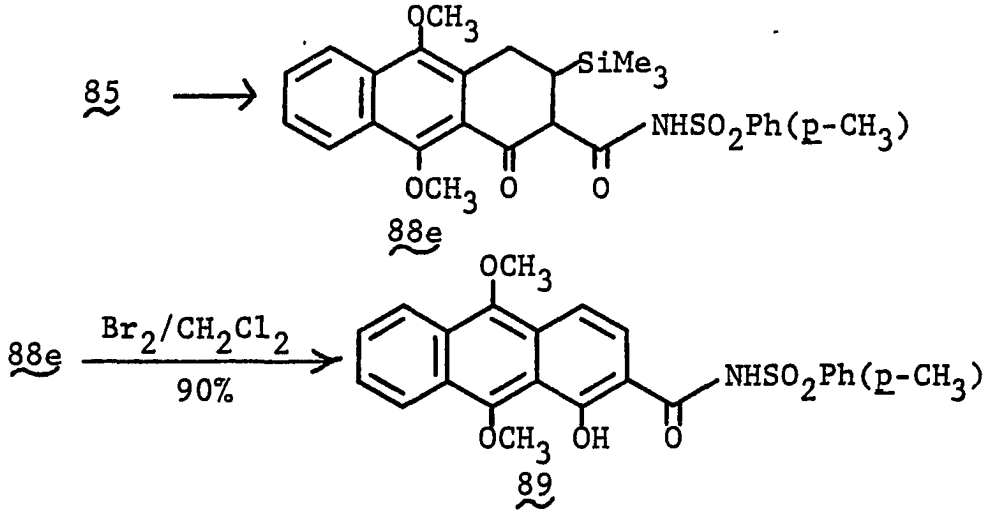
We then looked for an alternative synthetic application for 82. We had shown that the silyl group allowed a mild and high yield transformation of the ketone to a phenol (82 → 83). We decided to introduce a functional group alpha to the ketone which, after aromatization, would facilitate metalation of the ortho position and thus allow introduction of the desired functionality.

A number of oxygen and nitrogen containing functional groups have been shown to facilitate ortho metalation of an aromatic ring (68). We hoped to introduce such a group via the enolate of 82. While the synthesis of enol silyl ether

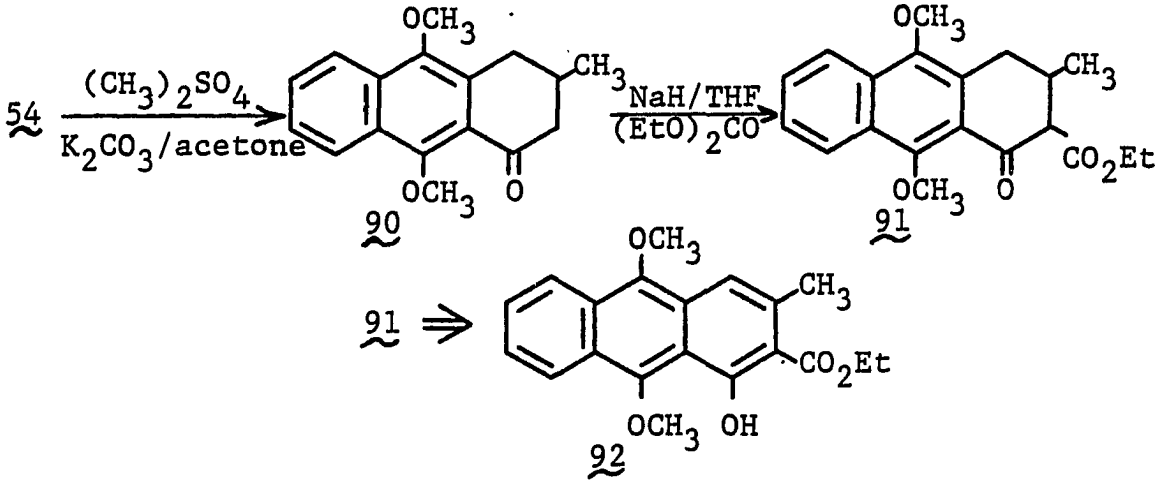


	X
88a	CHO
88b	CO_2R
88c	CH_2OH
88d	CH_2NR_2
88e	$CONHSO_2Ph(p\text{-}CH_3)$

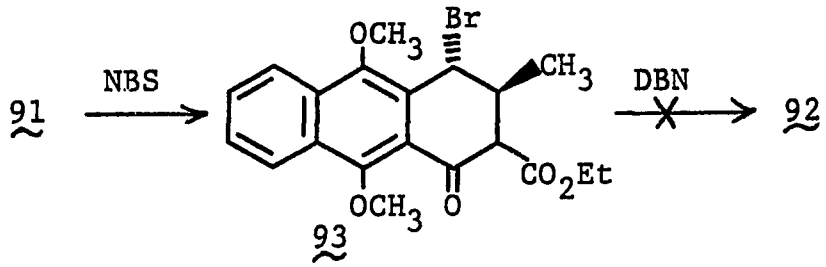
85 demonstrated that the enolate could be made, the enolate proved to be extremely unreactive. The enolate would not participate in aldol condensations, alkylations, acylations or Mannich reactions. Apparently, the steric bulk of the trimethylsilyl group hinders the approach of an electrophile to the enolate. In only one case, were we able to introduce a potentially suitable functional group alpha to the ketone. Under mild conditions, enol silyl ethers are known to react with sulfonyl isocyanates to give β-keto amides (69). Enol silyl ether 85 reacted with p-toluenesulfonyl isocyanate to give 88e. The ketone could be aromatized in excellent yield to the phenol 89. Diethyl amides are especially useful for promoting ortho metalation (68), but attempts to transform the sulfonyl amide into a diethyl amide by heating with diethyl amine or by conversion first to the acid were unsuccessful.



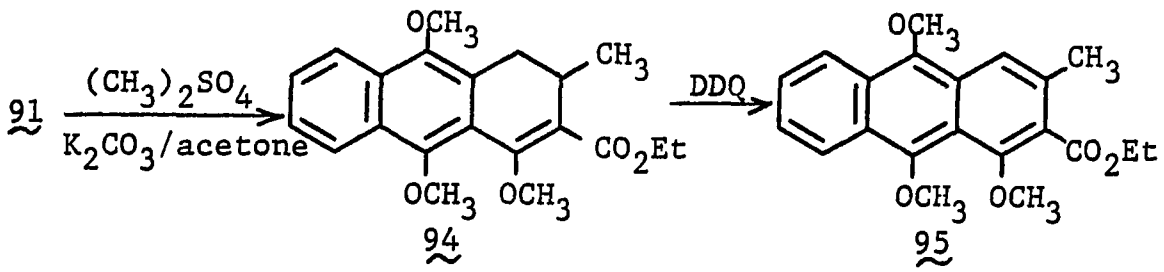
At this point it was decided that the trimethylsilyl group was more of a hindrance than a help. We then returned to tricyclic hydroquinone 54. The methyl group was not expected to hinder functionalization of the ketone. After formation of the dimethyl ether 90, the enolate could be easily acylated with diethyl carbonate to give 91.



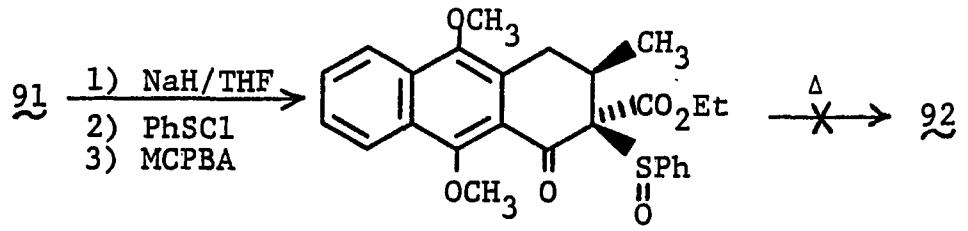
Finding a method for aromatization of 91 was much more difficult than we originally anticipated. Benzylic bromination, followed by treatment with DBN or quinoline did not give the desired phenol. The bromine must have added trans



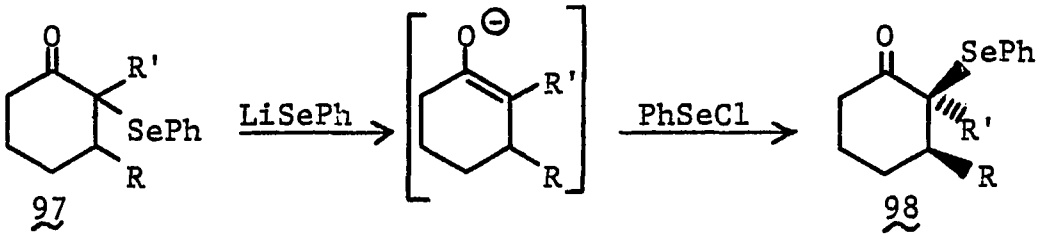
to the methyl group, thus, preventing the base promoted elimination. The α-bromoketone, formed by addition of Br_2 to 91, also did not give 92 when treated with base.



The methyl enol ether 94 could be aromatized by treatment with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) in only 33% yield. We felt that a thermal sulfoxide elimination should provide 92 in a much higher yield. Treatment of the sodium enolate of 91 with phenylsulfenyl chloride followed by oxidation gave the crude sulfoxide 96. After prolonged heating in high boiling solvents, none of the desired phenol was obtained. Apparently, the sulfide added

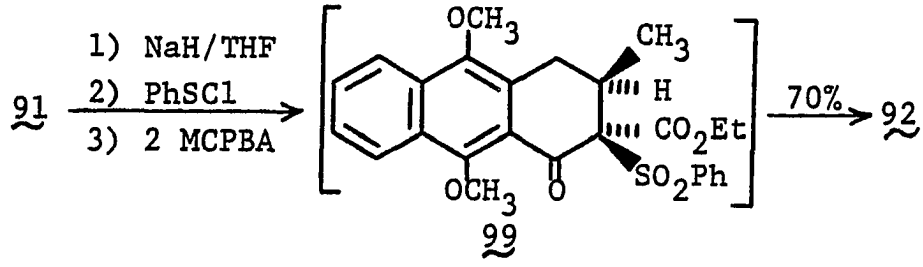


to the enolate from the same side as the methyl group. A cis hydrogen beta to the sulfoxide is necessary for the thermal elimination to occur. The stereochemical outcome of this type of addition has also been observed in similar systems (97 → 98) by Zima and coworkers (70).

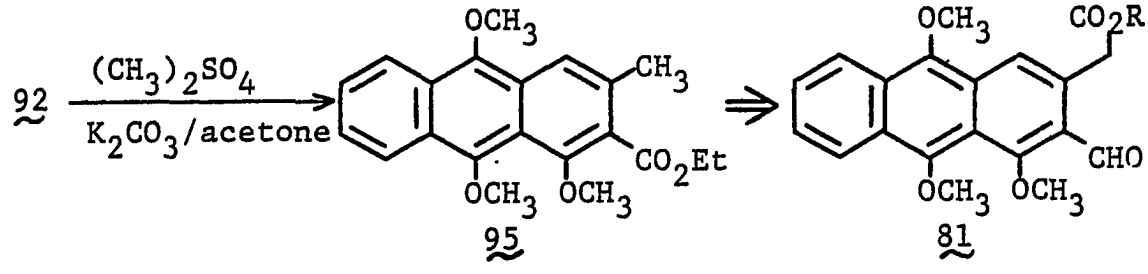


Knowing the stereochemistry of the intermediate α-keto sulfide, we thought that oxidation to the sulfone followed by a base induced trans elimination would yield the desired phenol. In fact, oxidation of the sulfide with two equivalents of MCPBA at room temperature or in refluxing THF provided phenol 92 directly. Oxidation at 0 °C gave only the sulfone 99. Sulfone 99 did not give 92 when heated with DBN, but when 99 was heated in the presence of m-chloro-benzoic acid the phenol was formed. Therefore, elimination

to give 92 is an acid promoted process. The acid is provided as the by-product of the oxidation. This afforded an extremely efficient one pot conversion of ketone 91 to phenol 92.

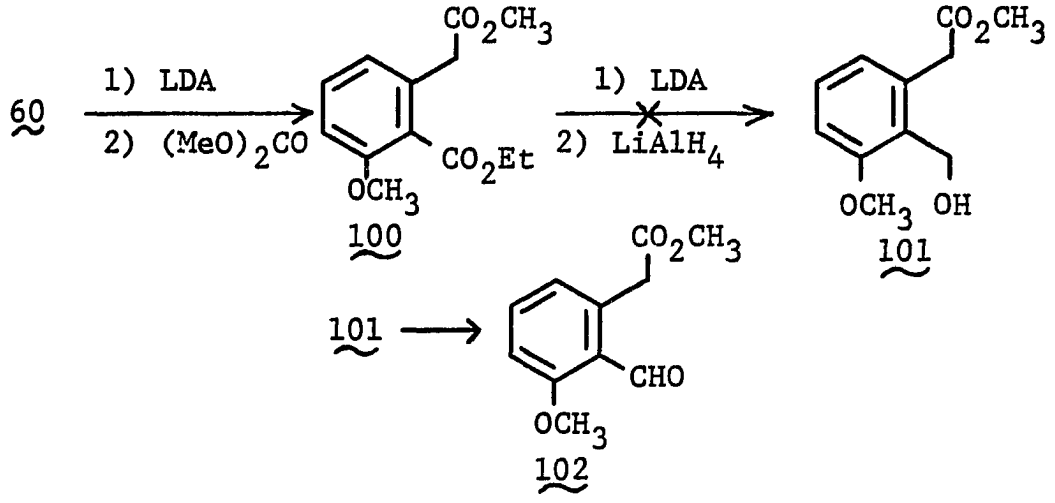


Having the tricyclic aromatic system 92 in hand, methods were investigated for transforming 95 into the desired key intermediate 81. Ethyl 2-methoxy-6-methyl benzoate (60) was used as a model system for the transformation. The ability

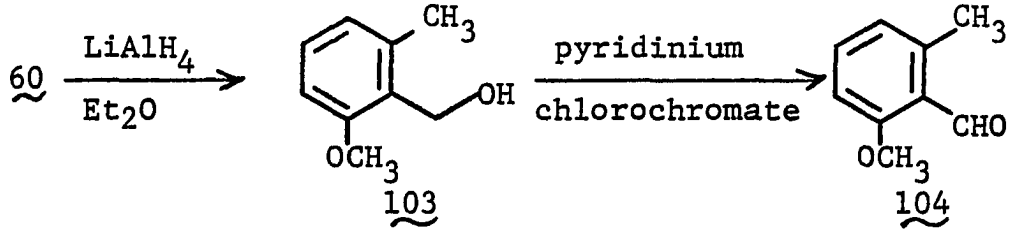


of the ester to stabilize carbanion formation (71) allowed synthesis of diester 100. Using a method developed in our laboratory for the selective reduction of esters in the presence of other carbonyl functionality (72), we hoped to selectively reduce the ethyl ester to an alcohol 101.

Careful oxidation would then yield the desired aldehyde ester 102. Unfortunately, only a small amount of the lactone derived from 101 could be isolated.

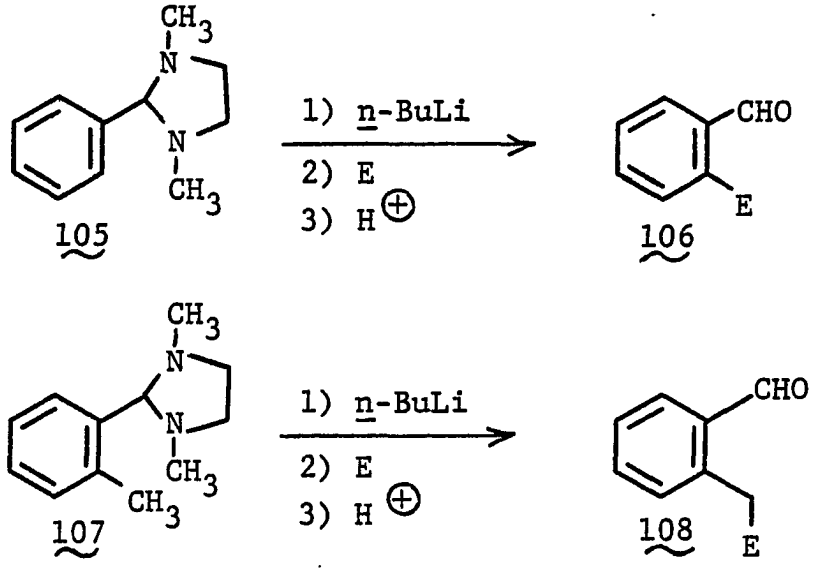


It is known that esters, nitriles and some amides will allow carbanion formation and subsequent functionalization of an ortho methyl group on an aromatic ring (68). The use of an aldehyde in this process has never been reported.

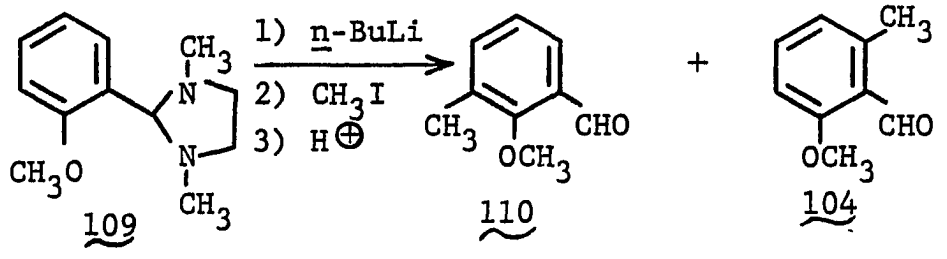


When aldehyde 104 was treated with LDA at -78 °C in THF, a dark colored solution resulted. This was indicative of anion formation. However, after addition of carbon dioxide only unreacted starting material was isolated.

A number of aldehyde derivatives have been used to allow metalation of an aromatic ring. The imidazolidine derivative has been reported to allow metalation on the ring (105 → 106) and on an ortho methyl group (107 → 108) (73).

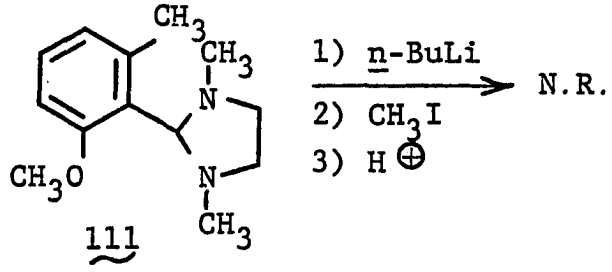


Attempted metalation of the aldehyde derivative 109, followed by addition of methyl iodide, gave 110 and a trace of the expected isomer 104. The conformation of the imidazoli-



dine ring that is necessary to allow metalation must not be attainable when an ortho substituent such as a methoxyl group is present. Because a methoxyl group can also facilitate

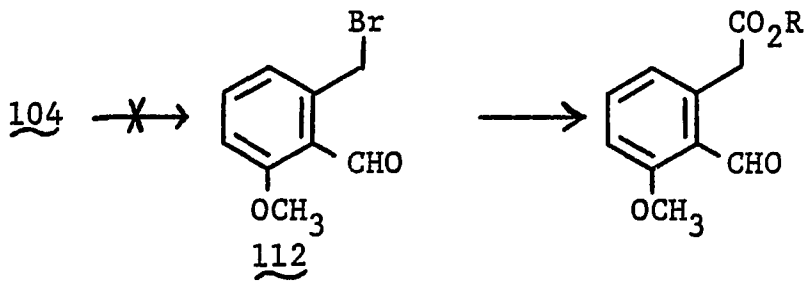
ortho metalation (68), the observed product was obtained. It was hoped that the necessary conformation of the imidazolidine was not so badly disturbed that the desired metalation might occur with aldehyde derivative 111. Unfortunately, no reaction occurred. While dimethyl acetals of aromatic



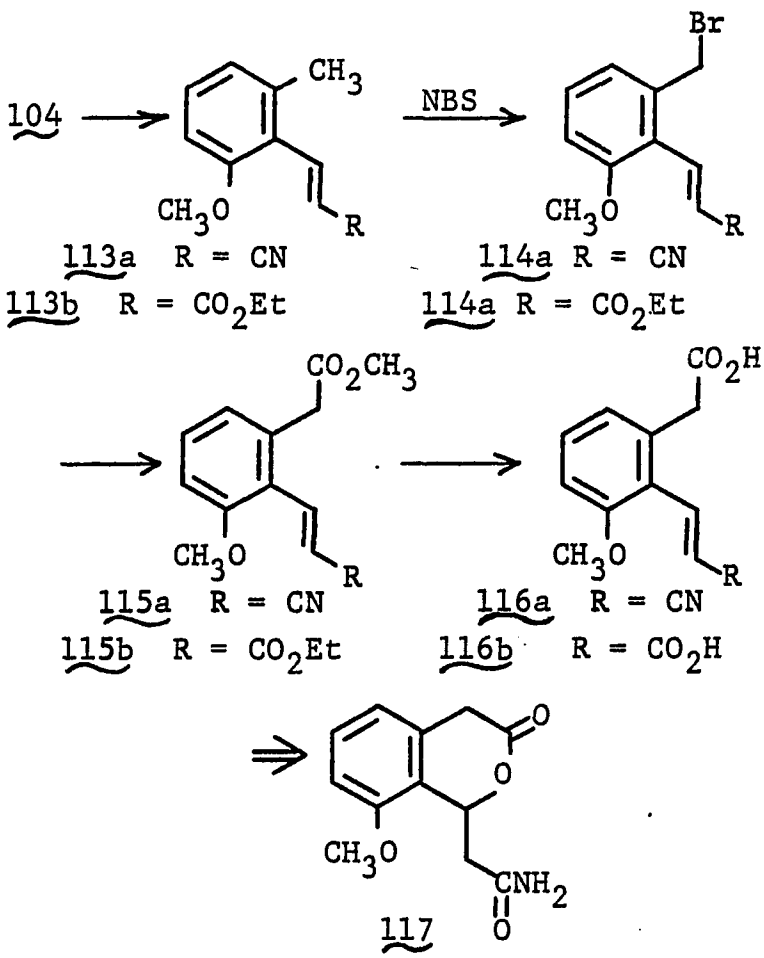
111

aldehydes have been used for ortho metalations, it has been reported that the presence of any functional group ortho to the acetal completely hinders the metalation (74). Again this must be due to steric factors.

At this point, it became obvious that carbanion chemistry would not allow the direct synthesis of 102. A recent result by Cowell and Stille (75) had shown that benzylic halides could be efficiently carboalkoxylated using a palladium catalyst. This would have been a nice method for obtaining the desired aldehyde ester. However, recent work by Cheung (76) had shown that when a variety of substituted tolualdehydes were treated with NBS, only acid bromides were isolated.

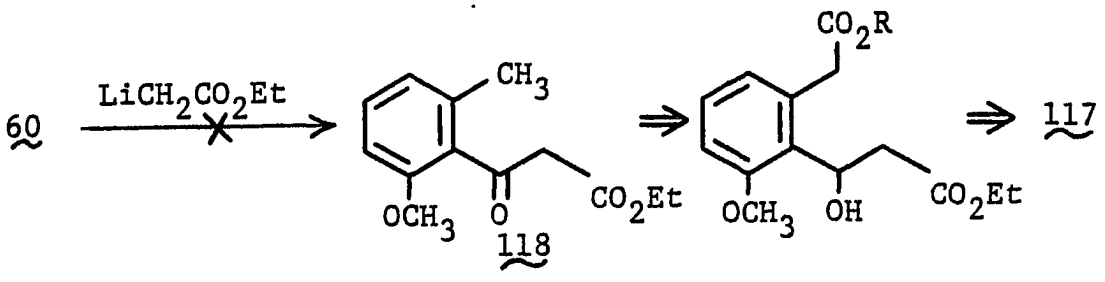


A Wittig reaction gave compounds 113a and 113b. Using the Cowell and Stille method, the ester could be introduced in good to excellent yield. Hydrolysis gave the acid nitrile



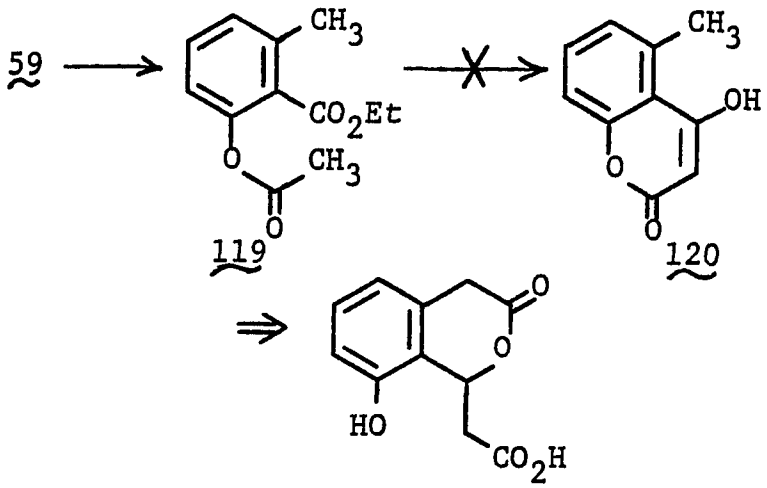
116a or the diacid 116b. It was hoped that after lactonization the acid or nitrile could be transformed into an amide. This would provide a model 117 for the AB ring system of deoxyekatetrone. Treatment of the acids 116a and 116b with base (77a) gave back starting material. Attempted bromolactonization (77b) resulted in ring halogenation. Selenolactonization (77c) and mercuric ion promoted lactonization (77d) also failed. Apparently, the unsaturated side chain is oriented perpendicular to the aromatic ring to avoid steric interactions with the two ortho substituents. This must make it difficult to attain the conformation necessary for lactonization.

A biomimetic route to the aklavinone AB ring system was next examined. The addition of the carbanion of ethyl acetate to 60 should give β-keto ester 118 which might further be transformed to 117. The benzylic hydrogens of

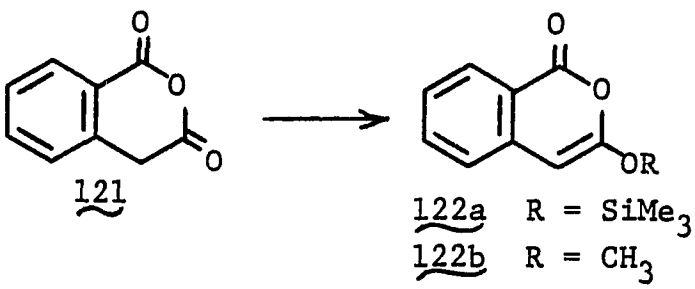


60 are sufficiently acidic that anion exchange occurred when 60 was added to excess lithio ethyl acetate. Only starting material was isolated. An intramolecular method for

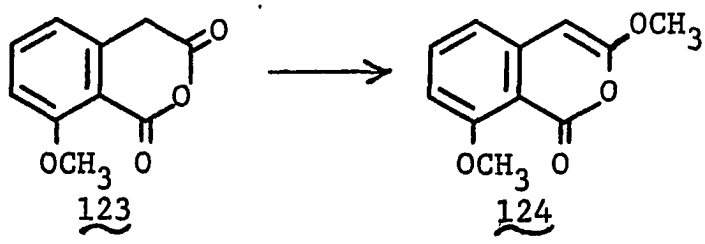
introducing a two carbon unit was also tried. The acetate of 59 was made. Attempts to use LDA to form coumarin 120 led to isolation of 59. Potassium hydride promoted cyclization also failed.



Compound 122a,b could be prepared from homophthalic anhydride 121. While 122a rapidly decomposed to the anhydride upon exposure to air, compound 122b was much more stable.

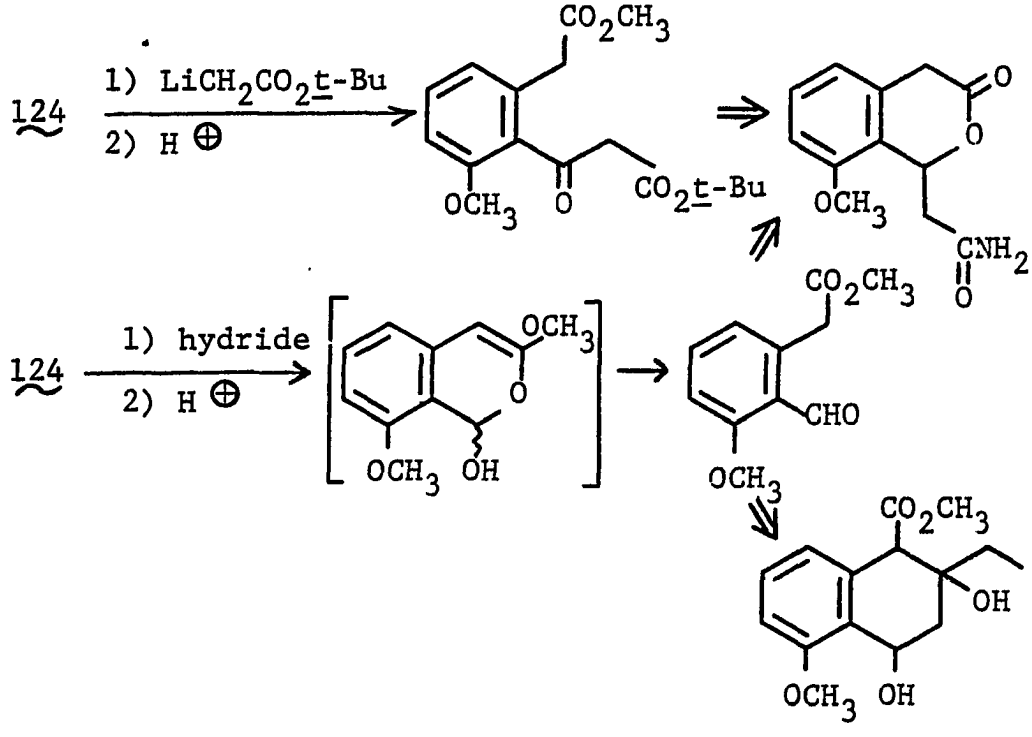


Extension of this reaction to anhydride 123 would give 124. Selective reactions at the unprotected carbonyl group will



123 124

provide a route to a B ring unit with the desired functionality. This will allow formation of the AB systems for deoxyaklavinone and deoxyekatetrone.



CONCLUSION

The utility of phthalide annelations for the rapid generation of polycyclic aromatic systems has been demonstrated. The 3-thiophenyl and 7-methoxy-3-cyano phthalides were successfully used for the first time in annelation reactions. The use of protected o-carboxymethyl cyanohydrins and an o-carboxyethyl thioacetal in the annelation process was also reported for the first time. A phthalide annelation initiated a very efficient two step synthesis of pachybasin. An intermediate in the pachybasin synthesis was functionalized to give a tricyclic aromatic system which should be useful for elaboration to both aklavinone and ekatetrone and their deoxy analogues. The annelation reaction of phthalides is especially applicable to the synthesis of 11-deoxyanthracyclines, but should also provide an efficient approach to the synthesis of other natural products containing quinones.

EXPERIMENTAL

Infrared spectra were obtained on a Beckman IR 4250 or Acculab 2 spectrometer. The NMR spectra were recorded using a Varian EM-360 or A-60 spectrometer. All chemical shifts are reported in δ relative to tetramethylsilane as an internal standard. The ^{13}C spectra were recorded using a Jeol FX-90Q spectrometer. The chemical shifts are reported in ppm relative to the central peak of $CDCl_3$ (77.06 ppm). An AEI-MS902 mass spectrometer was used for mass spectral data. Melting points were determined on a Fisher-Johns melting point apparatus and are uncorrected. Elemental analyses were performed by Galbraith Laboratories, Inc. Tetrahydrofuran and diethyl ether were distilled from $LiAlH_4$ prior to use.

Attempted Preparation of 3-Cyano Phthalide (31)

To a solution of 5.5 g (29 mmol) of crude 49 in 100 mL of $CHCl_3$ was added 20 g of silica gel (Davison 60-200 mesh, grade 62). The mixture was stirred at room temperature for 72 hours. The silica gel was filtered and the filtrate was concentrated to yield 3.92 g of a yellow solid. NMR (6.10 (s, 1 H)), IR (1790 cm^{-1}) and TLC comparison with authentic material (45) indicated that the major component of the crude product was the desired phthalide 31. No

unreacted cyanohydrin remained. An unidentifiable aromatic impurity could not be removed by recrystallization or chromatography.

Preparation of 3-Cyano-7-methoxy Phthalide (33)

To a solution of 6.57 g (30 mmol) of 61 in 60 mL of CCl_4 was added 5.34 g (30 mmol) of NBS and a few crystals of benzoyl peroxide. The mixture was refluxed for 16 hours. After cooling to room temperature, the mixture was filtered and the solvent was evaporated under reduced pressure to give the crude α-bromonitrile (NMR ($CDCl_3$) 1.40 (t, 3 H, J = 6 Hz), 4.40 (q, 2 H, J = 6 Hz), 6.88 (s, 1 H), 6.82-7.50 (m, 3 H)). The crude α-bromonitrile was placed in a one-necked flask equipped with a magnetic stirring bar and the pressure was reduced to 10 mm. The flask was then immersed in a preheated silicon oil bath (bath temperature 155 °C) and heated with stirring for 45 minutes. After cooling, the crude product was chromatographed on silica gel using hexane/ethyl acetate (3:2) as the solvent. Chromatography provided 2.78 g (14.7 mmol, 49%) of 33 (mp 147-148.5 °C). NMR (d_6-acetone/d_6-DMSO) 4.03 (s, 3 H), 6.58 (s, 1 H), 7.21-8.02 (m, 3 H). IR (Nujol) cm^{-1} 1785. High resolution mass spectrum for $C_{10}H_7NO_3$ requires 189.04260; measured 189.04205.

Preparation of 5-Trimethylsilyl-2-cyclohexen-1-one (40)

To a solution of 32.6 mL (300 mmol) of anisole and 153 mL (1200 mmol) of Me_3SiCl in 150 mL of THF was added 6.3 g (900 mmol) of lithium wire cut into small pieces. The mixture was stirred under N_2 at room temperature for 7-9 days, or until all of the lithium had dissolved. The mixture was filtered under N_2 and the THF and excess Me_3SiCl were distilled off under N_2. The crude product was immediately dissolved in 150 mL of H_2O/acetone (1:1) at 0 °C which had been adjusted to pH 2 by addition of dilute HCl. After stirring the solution overnight at room temperature, the acetone was evaporated under reduced pressure and the aqueous solution was extracted with methylene chloride. The organic solution was washed with brine, dried over Na_2SO_4 and concentrated to give a clear yellow oil. NMR and IR analysis showed that the product was a mixture of α,β and β,γ unsaturated ketones. The crude product was dissolved in 250 mL of acetone and 2 mL of concentrated HCl was added. The solution was refluxed overnight. After the solvent was evaporated, the residue was dissolved in methylene chloride and was washed with saturated sodium bicarbonate. The organic solution was then washed with brine, dried over Na_2SO_4 and concentrated in vacuo. Careful chromatography on silica gel using hexane/ether (5:1) as the solvent gave a pale yellow oil. The oil was Kugelrohr distilled (105 °C/10

mm) to give 23.3 g (139 mmol, 46%) of 40. NMR ($CDCl_3$) 0.05 (s, 9 H), 2.31-2.70 (m, 5 H), 6.20 (d, 1 H, J = 10 Hz), 7.25 (m, 1 H). IR (film) cm^{-1} 1675. High resolution mass spectrum for $C_9H_{16}OSi$ requires 168.09705; measured 168.09684.

Preparation of 3,4,4a,5,8,8a-Hexahydro-6-methyl-3-trimethylsilyl-1(2H)-naphthalenone (41)

To a solution of 3.36 g (20 mmol) of 40 in 20 mL of benzene was added 6.0 mL (60 mmol) of isoprene and 0.25 mL (2 mmol) of $BF_3 \cdot Et_2O$. The solution was stirred at room temperature for 7 days. The solution was concentrated to give an oil which was chromatographed on silica gel using hexane/ether (10:1) as the solvent. The reaction afforded 3.6 g (15.1 mmol, 75%) of 41. NMR ($CDCl_3$) 0.00 (s, 9 H), 1.60 (br s, 3 H), 1.70-2.90 (m, 11 H), 5.40 (m, 1 H). IR (film) cm^{-1} 1700. High resolution mass spectrum for $C_{14}H_{24}OSi$ requires 236.159649; measured 236.160853.

Preparation of 4,4a,5,8-Tetrahydro-6-methyl-1(8aH)-naphthalenone (42)

To a 1 M THF solution of 3.0 mmol of LDA (78) at -78 °C under N_2 was added 0.71 g (3.0 mmol) of 41 in 3 mL of THF. After stirring for 15 minutes at -78 °C, 0.16 mL (3.0 mmol) of bromine in 3 mL of methylene chloride was added and the solution was stirred for an additional one minute. The reaction was quenched by dilution with ether and washing

with 30 mL of water containing 3.0 mmol of acetic acid. The organic solution was washed with brine, dried over Na_2SO_4 and concentrated. The crude bromide 45 (0.8 g, 2.5 mmol) was immediately dissolved in 5 mL of acetonitrile. Potassium fluoride (0.24 g, 2.5 mmol) was added and the mixture was stirred overnight at room temperature. The mixture was diluted with ether and then was washed with water. The organic solution was dried over Na_2SO_4, filtered and concentrated in vacuo. The crude product was chromatographed on silica gel using hexane/ether (5:1) as the solvent. Chromatography gave 0.15 g (0.93 mmol, 34% overall yield) of 42. NMR ($CDCl_3$) 1.65 (br s, 3 H), 1.80-2.90 (m, 8 H), 5.40 (m, 1 H), 6.00 (d, 1 H, J = 10 Hz), 6.90 (m, 1 H). IR (film) cm^{-1} 3020, 1670. High resolution mass spectrum for $C_{11}H_{14}O$ requires 162.10447; measured 162.10444.

Attempted Preparation of 5-Carboethoxymethyl-2-cyclohexen-1-one from 5-Carboethoxymethyl-3-trimethylsilyl Cyclohexenone (43)

To a solution of 0.24 g (1.0 mmol) of 43 in 5 mL of chloroform/ethyl acetate (1:1) was added 0.45 g (2.0 mmol) of $CuBr_2$. The mixture was refluxed for 7 hours. The resulting solution was washed with 10% Na_2CO_3 and then with brine. The organic solution was dried over Na_2SO_4, filtered and concentrated in vacuo. The crude product contained no silyl

group. The NMR spectrum indicated the presence of a double bond, but the position of the double bond could not be determined from the spectrum. It was clear though that none of the desired enone was obtained.

Attempted Preparation of 6-Methoxy-6-methyl-2-decalen-1-one from 6-Methoxy-6-methyl-3-trimethylsilyl-1-decalone (44)

To a solution of 0.27 g (1.0 mmol) of 44 in 5 mL of chloroform/ethyl acetate (1:1) was added 0.45 g (2.0 mmol) of $CuBr_2$. The mixture was refluxed for 2 hours. The resulting solution was washed with 10% Na_2CO_3 and then with brine. The organic solution was dried over Na_2SO_4, filtered and concentrated in vacuo. The crude product contained no methoxyl group and the spectra were the same as those obtained from the product of the reaction of 41 with $CuBr_2$.

Preparation of 6-Thiophenyl-2-cyclohexen-1-one (48)

To a 1 M solution of 64 mmol of LDA at -78 °C under N_2 was added 5.8 mL (60 mmol) of 2-cyclohexen-1-one in 60 mL of THF. After stirring the mixture for 20 minutes at -78 °C, a 2 M THF solution of a mixture of 11.5 mL (90 mmol) of Me_3SiCl and 13.3 mL (90 mmol) of Et_3N was added. When the addition was complete, the reaction solution was allowed to warm to 0 °C and was stirred for 1 hour. The reaction mixture was poured into 350 mL of pentane and was rapidly

washed with cold 0.5 N HCl and then brine. The organic solution was dried over Na_2SO_4, filtered and concentrated in vacuo to give the enol silyl ether.

The crude enol silyl ether was dissolved in 120 mL of methylene chloride. The solution was cooled to -60 °C and 35.1 mL of a 1.71 M benzene solution of phenylsulfenyl chloride was added slowly. When the addition was complete, the solution was warmed to room temperature and was stirred for 1 hour. The solvent was evaporated and the residue was chromatographed on silica gel using hexane/ether (6:1) as the solvent. The reaction provided 7.25 g (35.5 mmol, 59%) of 48 as a viscous orange oil. NMR ($CDCl_3$) 1.80-2.80 (m, 4 H), 3.85 (m, 1 H), 6.00 (d, 1 H, J = 10 Hz), 6.90 (m, 1 H), 7.10-7.70 (m, 5 H). IR (film) cm^{-1} 3060, 1680.

Preparation of Phenylsulfenyl Chloride

To a suspension of 33.5 g (250 mmol) of N-chlorosuccinimide in 60 mL of benzene at 0 °C was slowly added dropwise a solution of 20.5 mL of benzenethiol in 40 mL of benzene. The mixture was stirred overnight at room temperature. The reaction mixture was filtered and the filtrate was concentrated in vacuo. The residue was distilled (87 °C/16 mm) to give a dark red oil (18.4 g, 127 mmol, 64%) that could be stored for several months at 0 °C as a solution in either methylene chloride or benzene.

Preparation of Methyl-1'-cyano-2-hydroxymethyl Benzoate (49)

To a solution of 5.7 g (55 mmol) of sodium bisulfite in 50 mL of water was added 8.2 g (50 mmol) of methyl-2-formyl benzoate (79). Ether (50 mL) was added and the solution was cooled to 0 °C. A solution of 2.7 g (55 mmol) of NaCN in 15 mL of water was added dropwise. After the mixture had been stirred for 1½ hours at 0 °C, the layers were separated and the aqueous layer was extracted with ether. The organic solution was washed with brine, dried over Na_2SO_4 and evaporated in vacuo. A waxy solid 49 (5.6 g, 29 mmol, 58%) was obtained. NMR ($CDCl_3$) 4.00 (s, 3 H), 5.88 (s, 1 H), 7.25-8.20 (m, 4 H). IR (Nujol) cm^{-1} 3350, 2255, 1715.

Preparation of 3-Thiophenyl Phthalide (50)

A few crystals of p-toluenesulfonic acid were added to a solution of 30.0 g (200 mmol) of o-carboxybenzaldehyde and 20.5 mL (200 mmol) of thiophenol in 200 mL of benzene. The solution was refluxed for 48 hours with removal of water in a Dean Stark trap. The solution was cooled and concentrated in vacuo to yield 47.4 g (196 mmol, 98%) of crystalline 50 (mp 101-102 °C, lit. (80) 100-102 °C). The product was sufficiently pure for immediate use. NMR ($CDCl_3$) 6.85 (s, 1 H), 7.30-8.00 (m, 9 H). IR ($CHCl_3$) cm^{-1} 1780.

General Procedure for the Reaction of 3-Thiophenyl Phthalide with Michael Acceptors; Preparation of 3,4-Dihydro-5,10-dihydroxy-3-methyl-1(2H)-anthracenone (54)

A solution of LDA·HMPA complex (81) was prepared by adding 10.4 mL (60 mmol) of HMPA in 20 mL of THF to a 1 M THF solution of LDA (45 mmol) at -78 °C under N_2. After the solution had been stirred for 20 minutes at -78 °C, a solution of 7.26 g (30 mmol) of 50 in 30 mL of THF was added dropwise to give a reddish-brown solution. After 30 minutes at -78 °C, a solution of 3.3 g (30 mmol) of 5-methyl cyclohexenone in 30 mL of THF was added dropwise. The solution was stirred for 1 hour at -78 °C and then 72 hours at 0 °C. The reaction mixture was then diluted with water, neutralized with dilute acetic acid and extracted with ethyl acetate. The organic solution was washed with brine, dried over Na_2SO_4, filtered and concentrated in vacuo. The residue was chromatographed on silica gel using hexane/ether as the solvent to yield 4.8 g (19.8 mmol, 66%) of 54 (mp 172-173 °C). NMR ($CDCl_3$) 1.15 (d, 3 H, J = 6 Hz), 2.00-3.45 (m, 5 H), 7.10-8.40 (m, 4 H). IR (Nujol) cm^{-1} 3220, 1610. High resolution mass spectrum for $C_{15}H_{14}O_3$ requires 242.094298; measured 242.09351.

2-Acetyl-1,4-dihydroxynaphthalene (51)

On an 8 mmol scale, compound 51 (mp 134-136 °C) was produced in 30% yield. NMR ($CDCl_3$) 2.57 (s, 3 H), 2.68

(s, 3 H), 7.30-8.60 (m, 4 H). IR (Nujol) cm^{-1} 3410, 1620. This material was identical to a sample prepared by an independent method (82).

3,4-Dihydro-5,10-dihydroxy-1(2H)-anthracenone (52)

On a 3 mmol scale, compound 52 (mp 169-171 °C) was obtained in 38% yield. NMR ($CDCl_3$) 1.90-3.20 (m, 6 H), 7.00-8.40 (m, 4 H). IR (Nujol) cm^{-1} 3320, 1620. High resolution mass spectrum for $C_{14}H_{12}O_3$ requires 228.07865; measured 228.07758. Compound 55 (54) was also produced in 32% yield from this reaction. NMR ($CDCl_3$) 1.70-3.00 (m, 9 H), 7.10-7.90 (m, 9 H). IR (Nujol) cm^{-1} 1780, 1715.

3,4-Dihydro-5,10-dihydroxy-3-trimethylsilyl-1(2H)-anthracenone (53)

On a 30 mmol scale, compound 53 (mp 150-152 °C) was prepared in 70% yield. NMR ($CDCl_3$) 0.10 (s, 9 H), 2.40-3.60 (m, 5 H), 7.40-8.60 (m, 4 H). IR (Nujol) cm^{-1} 3400, 1605. High resolution mass spectrum for $C_{17}H_{20}O_3Si$ requires 300.11818; measured 300.11817. Compound 56 was also produced in 5-10% yield from this reaction. NMR ($CDCl_3$) 0.05 (s, 9 H), 1.70-3.00 (m, 8 H), 7.10-7.90 (m, 9 H). IR(Nujol) cm^{-1} 1760, 1705.

Preparation of Pachybasin (57)

To a solution of 0.97 g (4 mmol) of hydroquinone 54 in 20 mL of CCl_4 was added 0.71 g (4 mmol) of NBS and a few

crystals of benzoyl peroxide. The mixture was refluxed for 10½ hours. On cooling to room temperature, a solid precipitated out of solution. The reaction mixture was diluted with ethyl acetate, washed with water and then brine, and dried over Na_2SO_4. The solvent was evaporated *in vacuo* and the residue was chromatographed on silica gel using hexane/methylene chloride (2:1) as the solvent to give 0.46 g (1.92 mmol, 48%) of pachybasin (mp 178-180 °C, lit. (55) 176-177 °C). NMR ($CDCl_3$) 2.40 (s, 3 H), 7.00-8.40 (m, 6 H). IR (Nujol) cm^{-1} 1670, 1640, 1590.

Preparation of Ethyl 2-Hydroxy-6-methyl Benzoate (60)

To a solution of 9.1 g (50 mmol) of ethyl 6-methyl-2-oxo cyclohex-3-ene carboxylate (57) in 100 mL of CCl_4 was added 8.9 g (50 mmol) of NBS and a few crystals of benzoyl peroxide. The mixture was refluxed for 18 hours. After the reaction mixture had cooled to room temperature, it was filtered and the solvent was evaporated *in vacuo*. Chromatography of the residue on silica gel using hexane/ether (30:1) as the solvent provided 7.2 g (40 mmol, 80%) of 59 (mp 39-40 °C). NMR ($CDCl_3$) 1.4 (t, 3 H, J = 6 Hz), 2.53 (s, 3 H), 4.38 (q, 2 H, J = 6 Hz), 6.58-7.38 (m, 3 H), 11.21 (s, 1 H). IR (Nujol) cm^{-1} 3400, 1655, 1605.

Preparation of Ethyl 2-Methoxy-6-methyl Benzoate (60)

To a solution of 11.0 g (61 mmol) of 59 in 800 mL of acetone was added 12.6 g (91.5 mmol) of potassium carbonate and 8.65 mL (91.5 mmol) of dimethyl sulfate. The mixture was refluxed for 16 hours. After cooling to room temperature, the reaction mixture was filtered and concentrated in vacuo. The residue was chromatographed on silica gel using hexane/ether (30:1) as the solvent. Chromatography afforded 10.9 g (56 mmol, 92%) of 60. NMR ($CDCl_3$) 1.34 (t, 3 H, J = 6 Hz), 2.29 (s, 3 H), 3.80 (s, 3 H), 4.35 (q, 2 H, J = 6 Hz), 6.60-7.30 (m, 3 H). IR (film) cm^{-1} 1725, 1585.

Preparation of Ethyl 2-Cyanomethyl-6-methoxy Benzoate (61)

To a solution of 22.6 g (116.4 mmol) of 60 in 230 mL of CCl_4 was added 20.8 g (117 mmol) of NBS and a few crystals of benzoyl peroxide. The mixture was refluxed for 8 hours. After cooling to room temperature, the mixture was filtered and the solvent was evaporated in vacuo to give the crude benzylic bromide (NMR ($CDCl_3$) 1.40 (t, 3 H, J = 6 Hz), 3.81 (s, 3 H), 4.40 (q, 2 H, J = 6 Hz), 4.49 (s, 2 H), 6.75-7.55 (m, 3 H)). To a solution of the crude benzylic bromide in 60 mL of 95% EtOH was added a solution of 6.88 g (140.4 g) of NaCN in 70 mL of H_2O. The resulting solution was refluxed for 4 hours. The EtOH was evaporated under reduced pressure and the aqueous residue

was extracted with ether. The ethereal solution was washed with brine and dried over Na_2SO_4. After evaporating the ether in vacuo, the residue was chromatographed on silica gel using hexane/ether (10:1) as the solvent. Chromatography gave 7.64 g (39.4 mmol) of unreacted 60 and 14.1 g (63.9 mmol) of 61. The corrected yield was 83%. NMR ($CDCl_3$) 1.40 (t, 3 H, J = 6 Hz), 3.75 (s, 2 H), 3.83 (s, 3 H), 4.40 (q, 2 H, J = 6 Hz), 6.82-7.50 (m, 3 H). IR (film) cm^{-1} 2225, 1725, 1580. High resolution mass spectrum for $C_{12}H_{13}NO_3$ requires 219.08955; measured 219.08945.

Preparation of Ethyl 4-Bromo-2-hydroxy-6-methyl Benzoate (63)

To a solution of 1.8 g (7 mmol) of ethyl 4-bromo-6-methyl-2-oxo cyclohex-3-ene carboxylate (62) (83) in 15 mL of CCl_4 was added 1.25 g (7 mmol) of NBS and a few crystals of benzoyl peroxide. The mixture was refluxed 24 hours. After cooling to room temperature, the reaction mixture was filtered and the solvent was evaporated in vacuo. The residue was dissolved in 10 mL of benzene and 1.8 mL (14 mmol) of DBN was added. The solution was refluxed overnight. On cooling to room temperature, the reaction mixture was diluted with water and acidified. The aqueous layer was extracted with ether and the combined organic extract was washed with brine and dried over Na_2SO_4. The solvent was evaporated under reduced pressure. Chromatography of the

residue on silica gel using hexane/ether (10:1) as the solvent gave 1.15 g (4.4 mmol, 63%) of 63 (mp 42.5-44 °C). NMR ($CDCl_3$) 1.40 (t, 3 H, J = 6 Hz), 2.45 (s, 3 H), 4.35 (q, 2 H, J = 6 Hz), 6.75 (br s, 1 H), 6.94 (br s, 1 H), 11.45 (s, 1 H). IR ($CHCl_3$) cm^{-1} 3300, 1660, 1600. High resolution mass spectrum for $C_{10}H_{10}BrO_3$ (loss of H) requires 257.98921; measured 257.98911.

Preparation of 3,4-Dihydro-5,10-dihydroxy-9-methoxy-3-trimethylsilyl-1(2H)-anthracenone (66)

Phthalide 33 was reacted with 5-trimethylsilyl cyclohexenone on a 3 mmol scale using the conditions for thiophenyl phthalide annelations. Chromatography provided 40% of 66 which could not be completely purified. NMR ($CDCl_3$) 0.50 (s, 9 H), 2.10-2.85 (m, 5 H), 4.02 (s, 3 H), 7.05-8.00 (m, 3 H), 12.80 (s, 1 H), 14.60 (s, 1 H). IR ($CHCl_3$) cm^{-1} 3400, 1625, 1580.

Preparation of Methyl 2-(1'-Cyano-3'-methyl-2',4'-dioxahexyl) Benzoate (70)

To a solution of 1.73 g (9.0 mmol) of 49 and 2.86 mL (30 mmol) of ethyl vinyl ether in 20 mL of methylene chloride was added 0.4 g of pyridinium p-toluene sulfonate. The mixture was stirred at room temperature overnight. The reaction mixture was then washed with brine and dried over Na_2SO_4. The solvent was evaporated in vacuo and the residue

was chromatographed on silica gel using hexane/ether (10:1) as the solvent. Chromatography gave 1.07 g (4.1 mmol, 46%) of 70 as a mixture of diastereomers. NMR ($CDCl_3$) 1.22 (t, 3 H, J = 7 Hz), 1.45 (dd, 3 H), 3.62 (m, 2 H), 3.99 (s, 3 H), 5.10 (m, 1 H), 6.52 (d, 1 H, J = 5 Hz), 7.10-8.22 (m, 4 H). IR (film) cm^{-1} 1725. High resolution mass spectrum for $C_{12}H_{12}NO_3$ (loss of OCH_2CH_3) requires 218.08172; measured 218.08130.

Preparation of Methyl 2-(1'-t-butyldimethylsilyloxy) Cyanomethyl Benzoate (71)

To a solution of 1.9 g (10 mmol) of 49 and 1.8 g (12 mmol) of t-butyldimethylsilyl chloride in 20 mL of acetonitrile was added 0.75 g (11 mmol) of imidazole. The solution was stirred overnight at room temperature. The reaction mixture was poured into 75 mL of pentane and was then washed with water and dried over Na_2SO_4. The solvent was evaporated and chromatography of the residue gave 1.42 g (4.7 mmol, 39%) of 71. NMR ($CDCl_3$) 0.15 (s, 3 H), 0.25 (s, 3 H), 0.93 (s, 9 H), 3.90 (s, 3 H), 6.50 (s, 1 H), 7.10-8.10 (m, 4 H). IR (film) cm^{-1} 1720.

Preparation of 3,4,4a,10a-Tetrahydro-5-cyano-5-(2'-methyl-1',3'-dioxapentyl)-3-methyl-1(2H),10-anthracenedione (72)

On a 4.07 mmol scale, compound 70 was reacted with 5-methyl cyclohexenone using the conditions for thiophenyl

phthalide annelations. Chromatography provided 46% of 72 (mp 165.5-166.5 °C). NMR ($CDCl_3$) 1.00 (d, 3 H, J = 6 Hz), 1.27 (t, 3 H, J = 7 Hz), 1.60 (d, 3 H, J = 5 Hz), 1.90-3.40 (m, 7 H), 3.62 (q, 2 H, J = 7 Hz), 5.23 (q, 1 H, J = 5 Hz), 7.20-8.10 (m, 4 H). IR ($CHCl_3$) cm^{-1} 1600. Anal calcd for $C_{20}H_{23}NO_4$: C, 70.36; H, 6.79; N, 4.10. Found C, 70.16; H, 6.88; N, 4.09.

Preparation of 3,4,4a,10-Tetrahydro-5-cyano-5-t-butyldimethylsilyloxy-3-methyl-1(2H),10-anthracenedione (73)

On a 4.66 mmol scale, compound 71 was reacted with 5-methyl cyclohexenone using the conditions for thiophenyl phthalide annelations. Chromatography afforded 21% of 73 (mp 182-183 °C). NMR ($CDCl_3$) 0.37 (s, 6 H), 1.00 (s, 9 H), 1.05 (d, 3 H), 1.85-3.15 (m, 7 H), 7.20-8.00 (m, 4 H). IR ($CHCl_3$) cm^{-1} 1600. Anal calcd for $C_{22}H_{29}NO_3Si$: C, 68.89; H, 7.62; N, 3.65; Si, 7.32. Found C, 69.20; H, 7.67; N, 3.54; Si, 7.44.

Preparation of 3,4,4a,10a-Tetrahydro-9-methoxy-5,5-bis-thiophenyl-1(2H),10-anthracenedione (75)

On a 5 mmol scale, methyl 2-bis-thiophenylmethyl-6-methoxy benzoate (71) was reacted with 5-methyl cyclohexenone using the conditions for thiophenyl phthalide annelations. Chromatography provided 37% of 75 (mp 172-173 °C). NMR ($CDCl_3$) 0.75 (d, 3 H, J = 6 Hz), 1.70-3.60

(m, 7 H), 3.95 (s, 3 H), 6.70-7.30 (m, 13 H). IR ($CHCl_3$) cm^{-1} 1590. High resolution mass spectrum for $C_{22}H_{20}O_3S$ (loss of C_6H_6S) requires 364.11333; measured 364.11250.

Preparation of Ethyl 2-Cyanomethyl-6-phenylsulfonyl-oxy Benzoate (79)

To a solution of 16.0 g (50 mmol) of 78 in 75 mL of CCl_4 was added 9.1 g (55 mmol) of NBS and a few crystals of benzoyl peroxide. The mixture was refluxed overnight. After cooling to room temperature, the mixture was filtered and the solvent was evaporated in vacuo. The crude benzylic bromide was then dissolved in 40 mL of 95% EtOH and a solution of 2.94 g (60 mmol) of NaCN in 40 mL of water was added. The mixture was refluxed for 6 hours. The EtOH was evaporated in vacuo and the aqueous solution was extracted with methylene chloride. The organic extract was dried over Na_2SO_4, filtered and concentrated in vacuo. Chromatography of the residue on silica gel using hexane/-ether (1:1) as the solvent provided 2.1 g (6.1 mmol, 12%) of 79 (mp 51-52 °C). NMR ($CDCl_3$) 1.33 (t, 3 H, J = 6 Hz), 3.87 (s, 2 H), 4.27 (q, 2 H, J = 6 Hz), 6.90-7.90 (m, 8 H). IR ($CHCl_3$) 2250, 1730. High resolution mass spectrum for $C_{17}H_{15}NO_5S$ required 345.06710; measured 345.06758.

Preparation of 3,4-Dihydro-5,10-dimethoxy-3-trimethylsilyl-1(2H)-anthracenone (82)

To a solution of 1.8 g (6.03 mmol) of 53 in 120 mL of acetone was added 2.04 mL (21.6 mmol) of dimethyl sulfate and 3.3 g (24 mmol) of potassium carbonate. The mixture was refluxed for 16 hours. On cooling to room temperature, the solution was filtered and solvent was evaporated in vacuo. Chromatography of the residue on silica gel using hexane/ether (10:1) as the solvent gave 1.8 g (5.5 mmol, 91%) of 82 (mp 98-100 °C). NMR ($CDCl_3$) 0.10 (s, 9 H), 2.20-3.60 (m, 5 H), 3.89 (s, 3 H), 4.00 (s, 3 H), 7.20-8.40 (m, 4 H). IR ($CHCl_3$) cm^{-1} 1625.

Preparation of 1-Hydroxy-5,10-dimethoxy Anthracene (83)

To a solution of 0.16 g (0.5 mmol) of 82 was added 0.09 g (0.5 mmol) of NBS and a crystal of benzoyl peroxide. The mixture was refluxed for 1 hour. After cooling to room temperature, the mixture was filtered and the solvent was evaporated in vacuo. The residue was chromatographed on silica gel using hexane/ether (3:1) as the solvent to afford 0.09 g (0.37 mmol, 74%) of 83. NMR ($CDCl_3$) 4.00 (s, 3 H), 4.03 (s, 3 H), 6.70-8.30 (m, 7 H), 9.75 (s, 1 H). IR (Nujol) cm^{-1} 3340, 1630. High resolution mass spectrum for $C_{16}H_{14}O_3$ requires 254.0943; measured 254.09427.

Preparation of 1-Hydroxy-5,10-anthracenedione (84)

To a solution of 0.13 g (0.5 mmol) of 83 in 3 mL of glacial acetic acid was added 0.5 mL of concentrated nitric acid. The solution was stirred for 10 minutes at room temperature and then was diluted with water. The mixture was extracted with methylene chloride and the organic solution was dried over Na_2SO_4 and then evaporated in vacuo to give a red solid. The product was recrystallized from EtOH to give fine orange needles of 84 (mp 185-187 °C, lit. (84) 188-189 °C). NMR ($CDCl_3$) 6.00-7.25 (m, 7 H), 12.50 (s, 1 H). IR (Nujol) cm^{-1} 1665, 1630, 1580.

Preparation of 3,4-Dihydro-5,10-dimethoxy-3-trimethysilyl-1-trimethylsilyloxy Anthracene (85)

To a 1 M THF solution of LDA (10 mmol) at -78 °C under N_2 was added dropwise a 1 M THF solution of 3.28 g (10 mmol) of 82. After the solution was stirred for 20 minutes at -78 °C, a 1 M THF solution of 1.9 mL (15 mmol) of trimethylsilyl chloride and 2.1 mL (15 mmol) of triethyl amine was added dropwise. The solution was allowed to warm to 0 °C and was stirred at that temperature for 1 hour. The reaction mixture was poured into 150 mL of pentane. The solution was washed with cold 0.5 N HCl and then brine. The organic phase was dried over Na_2SO_4, filtered and evaporated under reduced pressure to give a quantitative

yield of 85 as a viscous orange oil. NMR ($CDCl_3$) -0.08 (s, 9 H), 0.22 (s, 9 H), 3.04 (d, 2 H, J = 6 Hz), 3.75 (s, 3 H), 3.79 (s, 3 H), 5.36 (d, 1 H, J = 6 Hz), 7.12-8.10 (m, 4 H). IR (film) cm^{-1} 1620.

Preparation of 1-Hydroxy-5,10-dimethoxy-3-trimethylsilyl Anthracene (86)

To a solution of 1.6 g (4.0 mmol) of 85 in 10 mL of methylene chloride at -60 °C was added 4.0 mL of a 1 M methylene chloride solution of phenylsulfenyl chloride. After the addition was complete, the solution was stirred at room temperature for 40 minutes. The reaction mixture was cooled to -20 °C and 0.81 g (4.0 mmol) of 85% MCPBA was added rapidly. The solution was stirred for 1½ hours at -20 °C and was then washed with saturated sodium bicarbonate. The organic solution was washed with brine, dried over Na_2SO_4 and evaporated *in vacuo*. Chromatography of the residue on silica gel using hexane/ether (10:1) as the solvent provided 0.74 g (2.3 mmol, 57%) of 86 (mp 138-139 °C). NMR ($CDCl_3$) 0.40 (s, 9 H), 4.16 (s, 6 H), 7.10-8.60 (m, 6 H), 9.90 (s, 1 H). IR (Nujol) cm^{-1} 3320, 1615. High resolution mass spectrum for $C_{19}H_{22}O_3Si$ requires 326.133829; measured 326.13313.

Preparation of 1,5,10-Trimethoxy-3-trimethylsilyl Anthracene (87)

To a solution of 0.73 g (2.23 mmol) of 86 in 40 mL of acetone was added 0.76 mL (8.03 mmol) of dimethyl sulfate and 1.23 g (8.92 mmol) of potassium carbonate. The mixture was refluxed for 23 hours. After cooling to room temperature, the mixture was filtered and concentrated in vacuo. The residue was chromatographed on silica gel using hexane/ether (10:1) as the solvent. Chromatography provided 0.74 g (2.19 mmol, 98%) of 87 (mp 93-94 °C). NMR ($CDCl_3$) 0.40 (s, 9 H), 3.98 (s, 3 H), 4.05 (s, 6 H), 6.80-8.45 (m, 6 H). IR ($CHCl_3$) cm^{-1} 3000, 2960, 1600. High resolution mass spectrum for $C_{20}H_{24}O_3Si$ requires 340.14948; measured 340.14919.

Preparation of p-Toluenesulfonyl-3,4-dihydro-5,10-dimethoxy-3-trimethylsilyl-1(2H)-anthracenone-2-carboxamide (88e)

A solution of 4.0 g (10 mmol) of 85 in 3 mL of Et_2O was added dropwise to 1.55 mL (10 mmol) of p-toluenesulfonyl isocyanate. After the solution had stirred for 45 minutes at room temperature, the solvent was removed using an aspirator and 8 mL of MeOH was added. After stirring for 30 minutes at room temperature, the solution was concentrated. Recrystallization from hexane/ether gave 3.05 g (5.8 mmol, 58%) of 88e. NMR ($CDCl_3$) -0.27 (s, 9 H), 2.43

(s, 3 H), 2.50-3.50 (m, 4 H), 3.82 (s, 3 H), 4.02 (s, 3 H), 7.25-8.15 (m, 4 H). IR ($CHCl_3$) cm^{-1} 3250, 1665, 1630. High resolution mass spectrum for $C_{19}H_{24}O_3Si$ (loss of $CONHSO_2PhCH_3$) requires 328.1495; measured 328.15069.

Preparation of p-Toluenesulfonyl-1-hydroxy-5,10-dimethoxyanthracene-2-carboxamide (89)

To a solution of 2.6 g (4.94 mmol) of 88e in 20 mL of methylene chloride was added dropwise 4.94 mL of a 1 M methylene chloride solution of Br_2. The reaction mixture was stirred for 1 hour at room temperature and then concentrated in vacuo. Chromatography on silica gel using chloroform as the solvent provided 1.99 g (4.42 mmol, 90%) of 89. NMR ($CDCl_3$) 2.41 (s, 3 H), 4.01 (s, 3 H), 4.17 (s, 3 H), 7.20-8.35 (m, 6 H), 10.55 (br s, 1 H), 11.92 (s, 1 H). IR ($CHCl_3$) cm^{-1} 3300, 1680, 1630.

Preparation of 3,4-Dihydro-5,10-dimethoxy-3-methyl-1(2H)-anthracenone (90)

To a solution of 4.3 g (17.7 mmol) of 54 in 350 mL of acetone was added 5.0 mL (53 mmol) of dimethyl sulfate and 7.3 g (53 mmol) of potassium carbonate. The mixture was refluxed for 14 hours. After cooling to room temperature, the reaction mixture was filtered and concentrated in vacuo. Chromatography on silica gel using hexane/ether (10:1) gave 3.93 g (14.6 mmol, 82%) of 90 (mp 109-110 °C).

NMR ($CDCl_3$) 1.20 (d, 3 H, J = 5 Hz), 2.20-3.50 (m, 5 H), 3.90 (s, 3 H), 4.02 (s, 3 H), 7.40-8.45 (m, 4 H). IR (Nujol) cm^{-1} 1670. High resolution mass spectrum for $C_{17}H_{18}O_3$ requires 270.12560; measured 270.12565.

Preparation of 2-Carboethoxy-3,4-dihydro-5,10-dimethoxy-3-methyl-1(2H)-anthracenone (91)

To a suspension of 0.61 g (25.4 mmol) of oil free NaH in 20 mL of THF was added 3.1 mL (25.4 mmol) of diethyl carbonate, followed by dropwise addition of a 1 M THF solution of 3.43 g (12.7 mmol) of 90. The mixture was refluxed for 48 hours. After cooling to room temperature, the reaction mixture was diluted with water and neutralized with 1 N HCl. The aqueous phase was extracted with ethyl acetate and the combined organic phases were washed with brine and dried over Na_2SO_4. Evaporation of the solvent in vacuo, followed by chromatography on silica gel using hexane/ether (10:1) as the solvent afforded 3.74 g (10.9 mmol, 86%) of 91 as a mixture of diastereomers. NMR ($CDCl_3$) 0.97 (d, 3 H, J = 6 Hz), 1.34 (m, 3 H), 2.40-3.40 (m, 4 H), 3.90 (s, 3 H), 4.02 (s, 3 H), 4.15 (m, 2 H), 7.25-8.40 (m, 4 H). IR (film) cm^{-1} 1745, 1685, 1640, 1610.

Preparation of 2-Carboethoxy-1-hydroxy-5,10-dimethoxy-3-methyl Anthracene (92)

To a suspension of 0.072 g (3 mmol) of oil free NaH in 8 mL of THF was added dropwise a 1 M THF solution of 1.03 g (3 mmol) of 91. After the solution had been stirred for 30 minutes at room temperature, 2.36 mL (3 mmol) of a 1.27 M benzene solution of phenylsulfenyl chloride was added. The reaction mixture was heated to 60-70 °C and then a 1 M THF solution of 1.34 g (6.6 mmol) of 85% MCPBA was added rapidly, causing the solution to reflux vigorously. The solution was heated enough to maintain refluxing for 15 minutes. After the reaction mixture had cooled to room temperature, it was diluted with methylene chloride and washed with saturated sodium bicarbonate. The organic solution was washed with brine, dried over Na_2SO_4 and evaporated *in vacuo*. The residue was chromatographed on silica gel using hexane/ether (15:1) as the solvent. Chromatography provided 0.7 g (2.1 mmol, 70%) of 92 (mp 122-123.5 °C). NMR ($CDCl_3$) 1.40 (t, 3 H, J = 7 Hz), 2.56 (s, 3 H), 4.00 (s, 3 H), 4.03 (s, 3 H), 4.40 (q, 2 H, J = 7 Hz), 7.12-8.30 (m, 5 H), 12.36 (br s, 1 H). 90 MHz C-13 NMR ($CDCl_3$) 14.373, 23.475, 61.583, 62.883, 64.119, 109.575, 113.997, 122.321, 123.167, 125.443, 126.483, 126.938, 127.198, 133.441, 147.358, 150.870, 160.169, 171.355. IR ($CHCl_3$) cm^{-1} 3290, 1710, 1640, 1615. Oxidation as above,

except that the temperature was maintained at 0 °C, provided crude sulfone 99 (IR (film) cm^{-1} 1730, 1680, 1620, 1360). Treatment of 99 with DBN in benzene provided none of the desired phenol 92.

Attempted Preparation of 92 From 4-Bromo-2-carboethoxy-3,4-dihydro-5,10-dimethoxy-3-methyl-1(2H)-anthracenone (93)

To a solution of 0.51 g (1.5 mmol) of 91 in 5 mL of CCl_4 was added 0.27 g (1.5 mmol) of NBS and a few crystals of benzoyl peroxide. The mixture was refluxed for 8 hours. On cooling to room temperature, the mixture was filtered and the solvent was evaporated to give the crude benzylic bromide 93 (NMR 4.10 (d, 1 H, J = 2 Hz)). To a solution of the crude bromide in 5 mL of benzene was added 0.5 g (4 mmol) of DBN. The mixture was refluxed overnight. After cooling to room temperature, the solution was diluted with water and was then washed with 1 N HCl. The organic solution was washed with brine and dried over Na_2SO_4. The solvent was evaporated *in vacuo*. NMR analysis of the crude product indicated that none of the desired product 92 was present.

Attempted Preparation of 92 From 2-Carboethoxy-3,4-dihydro-5,10-dimethoxy-3-methyl-1(2-phenylsulfinyl)-anthracenone (96)

To a suspension of 0.048 g (2 mmol) of oil free NaH in 8 mL of THF was added a 1 M THF solution of 0.68 g (2 mmol) of 91. After the mixture had been stirred for 30 minutes

at room temperature, 1.57 mL (2 mmol) of a 1.27 M benzene solution of phenylsulfenyl chloride was added dropwise. Immediately after the addition was complete the solution was cooled to -20 °C and 0.43 g (2.1 mmol) of 85% MCPBA was added. The solution was stirred at -20 °C for another 20 minutes and then it was diluted with water and washed with saturated sodium bicarbonate. The organic phase was washed with brine, dried over Na_2SO_4 and evaporated *in vacuo* to give the crude sulfoxide **96** (IR (film) cm^{-1} 1740, 1680, 1640, 1615, 1060). The crude sulfoxide was refluxed overnight in both toluene and xylene, but none of the desired phenol **92** was obtained.

Preparation of 2-Carboethoxy-3,4-dihydro-1,5,10-trimethoxy-3-methyl Anthracene (**94**)

To a solution of 0.58 g (1.7 mmol) of **91** in 30 mL of acetone was added 0.25 mL (2.6 mmol) of dimethyl sulfate and 0.36 g (2.6 mmol) of potassium carbonate. The mixture was refluxed for 13 hours. After cooling to room temperature, the mixture was filtered and the solvent was evaporated *in vacuo*. Chromatography on silica gel using hexane/ether (10:1) as the solvent provided 0.69 g (1.7 mmol, 100%) of **94**. NMR ($CDCl_3$) 1.40 (t, 3 H, *J* = 7 Hz), 2.80-3.30 (m, 3 H), 3.75 (s, 3 H), 3.90 (s, 6 H), 4.35 (q, 2 H, *J* = 7 Hz), 7.25-8.40 (m, 4 H). IR (film) cm^{-1} 1710, 1690, 1615.

Preparation of 2-Carboethoxy-1,5,10-trimethoxy-3-methyl Anthracene (95) from 94

To a solution of 0.71 g (2 mmol) of 94 in 6 mL of benzene was added 0.5 g (2.2 mmol) of DDQ. The mixture was refluxed for 6 hours. After cooling to room temperature, the mixture was filtered and the solvent was evaporated in vacuo. Chromatography on silica gel using hexane/ether (10:1) as the solvent gave 0.23 g (0.65 mmol, 33%) of 95 (mp 93-94 °C). NMR ($CDCl_3$) 1.40 (t, 3 H, J = 7 Hz), 2.50 (s, 3 H), 4.00 (s, 6 H), 4.03 (s, 3 H), 4.45 (q, 2 H, J = 7 Hz), 6.95-8.50 (m, 5 H). 90 MHz C-13 NMR ($CDCl_3$) 14.308, 15.608, 19.767, 61.128, 62.753, 63.598, 63.794, 72.312, 118.419, 122.061, 122.906, 123.167, 125.182, 125.378, 125.768, 125.898, 126.093, 128.629, 128.824, 131.230, 168.168. IR ($CHCl_3$) cm^{-1} 1715, 1620.

Preparation of 95 from 92

To a solution of 2.03 g (5.97 mmol) of 92 in 20 mL of acetone was added 0.85 mL (9 mmol) of dimethyl sulfate and 1.24 g (9 mmol) of potassium carbonate. The mixture was refluxed for 14 hours. After cooling to room temperature, the reaction mixture was filtered and the solvent was evaporated in vacuo. Chromatography on silica gel using hexane/ether (15:1) as the solvent afforded 1.93 g

(5.5 mmol, 91%) of 92. This material was identical to the product prepared by DDQ oxidation of 94.

Preparation of Methyl 2-(2'-Carboethoxy-3'-methoxy phenyl) Acetate (100)

To a 1 M THF solution of 60 mmol of LDA at -78 °C under N_2 was added dropwise a 1 M THF mixture of 3.88 g (20 mmol) of 60 and 3.4 mL (40 mmol) of dimethyl carbonate. After the addition was complete, the reaction mixture was allowed to warm to room temperature and was stirred for 3½ hours. The solution was then diluted with water and neutralized with dilute HCl. The aqueous phase was extracted with methylene chloride. The organic extracts were combined and washed with brine, dried over Na_2SO_4 and concentrated in vacuo. Chromatography on silica gel using hexane/ether (10:1) as the solvent provided 4.04 g (16 mmol, 80%) of 100. NMR ($CDCl_3$) 1.34 (t, 3 H, J = 7 Hz), 3.66 (s, 5 H), 3.82 (s, 3 H), 4.47 (q, 2 H, J = 7 Hz), 6.80-7.45 (m, 3 H). IR (film) cm^{-1} 1745, 1590.

Attempted Preparation of Methyl 2-(2'-Hydroxymethyl-3'-methoxy phenyl) Acetate (101)

To a 1 M THF solution of 1.5 mmol of LDA at -78 °C under N_2 was added a 1 M THF solution of 0.38 g (1.5 mmol) of 100. The solution was stirred for 30 minutes at -78 °C and then 0.114 g (3 mmol) of $LiAlH_4$ was added. The reaction

mixture was allowed to warm to 0 °C and was stirred for 1 hour. The mixture was then poured into 50 mL of 3 N HCl. The aqueous mixture was extracted with ether. The organic solution was washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. Based on NMR and IR analysis of the crude product, none of the desired hydroxyacid was obtained. Only a small amount of the lactone produced by acid induced lactonization of the hydroxyacid was isolated.

Preparation of 2-Methoxy-6-methyl Benzyl Alcohol (103)

To a suspension of 1.14 g (30 mmol) of $LiAlH_4$ in 60 mL of Et_2O at 0 °C was added dropwise a solution of 5.82 g (30 mmol) of 60 in 25 mL of Et_2O. After the addition was complete, the reaction mixture was stirred for 3 hours at room temperature. Excess $LiAlH_4$ was destroyed by very careful addition of water at 0 °C. The reaction mixture was acidified with 6 N HCl and then extracted with ether. The organic solution was washed with brine, dried over Na_2SO_4 and evaporated *in vacuo*. The crude product was Kugelrohr distilled (110 °C/4 mm) to give 3.91 g (25.7 mmol, 86%) of 103 (mp 48.5-49.5 °C). NMR ($CDCl_3$) 2.35 (s, 3 H), 3.80 (s, 3 H), 4.67 (br s, 2 H); 6.50-7.23 (m, 3 H). IR ($CHCl_3$) cm^{-1} 3600, 3450, 1585. High resolution mass spectrum for $C_9H_{12}O_2$ requires 152.08373; measured 152.08355.

Preparation of 2-Methoxy-6-methyl Benzaldehyde (104)

To a suspension of 10.7 g (49.5 mmol) of pyridinium chlorochromate (PCC) in 60 mL of methylene chloride was rapidly added a solution of 5.0 g (33 mmol) of 103. The mixture was stirred at room temperature for 2 hours. Ether was added to the reaction mixture and the solvent was decanted. The residue in the flask was washed twice with ether. The combined ether washes were filtered through a pad of Celite and then concentrated in vacuo. The crude product was passed through a short column of silica gel to give 4.66 g (31 mmol, 94%) of 104 (mp 37-38 °C). NMR ($CDCl_3$) 2.52 (s, 3 H), 3.90 (s, 3 H), 6.67-7.45 (m, 3 H), 10.60 (s, 1 H). IR ($CHCl_3$) cm^{-1} 2780, 1680. High resolution mass spectrum for $C_9H_{10}O_2$ requires 150.06808; measured 150.067945.

Preparation of 1,3-Dimethyl-2-(2'-methoxy phenyl) Imidazoline (109)

To a solution of 4.07 g (30 mmol) of 2-methoxybenzaldehyde in 40 mL of benzene was added 2.8 g (31.8 mmol) of N,N'-dimethyl ethylene diamine, a few crystals of p-toluenesulfonic acid and some 3 Å molecular sieves. The mixture was refluxed for 48 hours. After cooling to room temperature, the solvent was decanted and the reaction flask was rinsed once with benzene. The solvent was

evaporated *in vacuo* and the residue was Kugelrohr distilled (105 °C/0.9 mm, lit. (85) 83 °C/0.2 mm) to provide 5.6 g (27 mmol, 90%) of 109. NMR ($CDCl_3$) 2.20 (s, 6 H), 2.60 (m, 2 H), 3.35 (m, 2 H), 3.78 (s, 3 H), 4.08 (s, 1 H), 6.70-7.80 (m, 4 H).

Attempted Preparation of 2-Methoxy-6-methyl Benzaldehyde (104) from 109

To a solution of 0.62 g (3 mmol) of 109 in 20 mL of Et_2O was added 1.36 mL (9 mmol) of N,N,N',N'-tetramethylethylene diamine (TMEDA), followed by dropwise addition of 4.3 mL (9 mmol) of a 2.1 M hexane solution of *n*-BuLi. After the mixture had been stirred for 7 hours at room temperature, 3 mL (48 mmol) of methyl iodide was added. The mixture was stirred for 15 minutes and then the reaction was quenched by addition of 50 mL of 2 N HCl. After stirring for 10 minutes, the solution was extracted with chloroform. The organic solution was washed with brine, dried over $NaSO_4$ and concentrated *in vacuo*. NMR analysis of the crude product indicated that a trace of aldehyde 104 had been obtained. Over 90% of the crude product was assigned the structure of compound 110. NMR ($CDCl_3$) 2.32 (s, 3 H), 3.88 (s, 3 H), 6.70-7.80 (m, 3 H), 10.32 (s, 1 H).

Preparation of 1,3-Dimethyl-2-(2'-methoxy-6'-methyl phenyl) Imidazolidine (111)

To a solution of 0.41 g (2.7 mmol) of 104 in 7 mL of benzene was added 0.35 g (4.8 mmol) of N,N'-dimethyl ethylene diamine, two crystals of p-toluene sulfonic acid and some 3 Å molecular sieves. The mixture was refluxed for 48 hours. After cooling to room temperature, the solvent was decanted and the reaction flask was rinsed with benzene. The solvent was evaporated in vacuo and the residue was Kugelrohr distilled (~110 °C/0.9 mm) to provide 0.46 g (2.1 mmol, 78%) of 111. NMR ($CDCl_3$) 2.16 (s, 6 H), 2.48 (m, 2 H), 2.58 (s, 3 H), 3.30 (m, 2 H), 3.76 (s, 3 H), 4.25 (s, 1 H), 6.57-7.25 (m, 3 H).

Preparation of 2-Methoxy-6-methyl Cinnamonitrile (113a)

To a suspension of 1.03 g (43 mmol) of oil free NaH in 50 mL of THF was added 6.55 mL (40.5 mmol) of diethyl cyanomethylphosphonate. After the mixture had stirred for 1 hour at room temperature, a 1 M THF solution of 6.07 g (40.5 mmol) of 104 was added dropwise. The mixture was stirred overnight at room temperature and then it was diluted with water. The aqueous solution was extracted with ether. The organic extract was washed with brine, dried over Na_2SO_4 and evaporated in vacuo. The crude product was passed through a short column of silica gel to

provide 6.3 g (36.4 mmol, 90%) of 113a. NMR ($CDCl_3$) 2.30 (s, 3 H), 3.80 (s, 3 H), 6.15 (d, 1 H, J = 17 Hz), 6.55-7.25 (m, 3 H), 7.40 (d, 1 H, J = 17 Hz). IR ($CHCl_3$) cm^{-1} 2205, 1610, 1595.

Preparation of Ethyl 2-Methoxy-6-methyl Cinnamate (113b)

To a solution of 3.98 g (26.5 mmol) of 104 in 50 mL of benzene was added 10.2 g (29.2 mmol) of carboethoxymethylene-triphenylphosphorane. The solution was refluxed for 15 hours. After cooling to room temperature, the solvent was evaporated *in vacuo* and the residue was diluted with hexane. The resulting suspension was filtered and the precipitate was washed with hexane. The combined filtrates were concentrated *in vacuo*. The crude product was passed through a short column of silica gel to provide 5.81 g (26.4 mmol) of 113b. NMR ($CDCl_3$) 1.30 (t, 3 H, J = 7 Hz), 2.43 (s, 3 H), 3.85 (s, 3 H), 4.20 (q, 2 H, J = 7 Hz), 6.52 (d, 1 H, J = 16 Hz), 6.60-7.30 (m, 3 H), 7.80 (d, 1 H, J = 16 Hz). IR (film) cm^{-1} 1710, 1630. High resolution mass spectrum for $C_{13}H_{16}O_3$ requires 220.10995; measured 220.10922.

Preparation of 1-Bromomethyl-6-methoxy Cinnamonitrile (114a)

To a solution of 6.3 g (36.4 mmol) of 113a in 70 mL of CCl_4 was added 13.0 g (72.8 mmol) of NBS and a few crystals of benzoyl peroxide. The mixture was refluxed for 72 hours.

After cooling to room temperature, the reaction mixture was filtered and the solvent was evaporated *in vacuo*. Chromatography on silica gel using hexane/ether (7:1) as the solvent gave 6.44 g (25.6 mmol, 70%) of 114a (mp 78-80 °C). NMR ($CDCl_3$) 3.86 (s, 3 H), 4.46 (s, 2 H), 6.28 (d, 1 H, J = 17 Hz), 6.65-7.35 (m, 3 H), 7.50 (d, 1 H, J = 17 Hz). IR ($CHCl_3$) cm^{-1} 2230, 1620, 1600, 1580. High resolution mass spectrum for $C_{11}H_{10}BrNO$ requires 250.99457; measured 250.99565.

Preparation of Ethyl 1-Bromomethyl-6-methoxy Cinnamate (114b)

To a solution of 5.72 g (26 mmol) of 113b in 30 mL of CCl_4 was added 9.2 g (52 mmol) of NBS and a few crystals of benzoyl peroxide. The mixture was refluxed for 96 hours. After cooling to room temperature, the reaction mixture was filtered and the solvent was evaporated *in vacuo*. Chromatography on silica gel using hexane/ether (10:1) provided 3.3 g (11.1 mmol, 43%) of 114b (mp 74-75 °C). NMR ($CDCl_3$) 1.33 (t, 3 H, J = 7 Hz), 3.85 (s, 3 H), 4.24 (q, 2 H, J = 7 Hz), 4.55 (s, 2 H), 6.63 (d, 1 H, J = 16 Hz), 6.70-7.40 (m, 3 H), 7.82 (d, 1 H, J = 16 Hz). IR ($CHCl_3$) cm^{-1} 1700, 1625, 1590, 1570. High resolution mass spectrum for $C_{13}H_{15}BrO_3$ requires 298.02046; measured 298.02153.

Preparation of 2-Carbomethoxymethyl-6-methoxy Cinnamonitrile (115a)

Bis-(triphenylphosine)palladium(II) chloride (0.02 g) and 0.51 g (3.72 mmol) of potassium carbonate were placed in a three-necked flask. The flask was evacuated and a balloon filled with carbon monoxide gas was attached. After allowing the flask to fill with carbon monoxide, 5 mL of THF and 1 mL of MeOH were added. A 1 M THF solution of 0.89 g (3.54 mmol) of 114a was added and the reaction mixture was stirred for 24 hours at room temperature. The mixture was filtered and concentrated in vacuo. The crude product was passed through a short column of silica gel to afford 0.67 g (2.92 mmol, 82%) of 115a. NMR ($CDCl_3$) 3.70 (s, 3 H), 3.86 (s, 3 H), 6.22 (d, 1 H, J = 17 Hz), 6.75-7.40 (m, 3 H), 7.44 (d, 1 H, J = 17 Hz). IR (film) cm^{-1} 2200, 1730, 1610, 1590, 1570. High resolution mass spectrum for $C_{13}H_{13}NO_3$ requires 231.08954; measured 231.08955.

Preparation of Ethyl 2-Carbomethoxymethyl-6-methoxy Cinnamate (115b)

Bis-(triphenylphosphine)palladium(II) chloride (0.06 g) and 1.55 g (11.2 mmol) of potassium carbonate were placed in a three-necked flask. The flask was evacuated and a balloon filled with carbon monoxide gas was attached. After allowing the flask to fill with carbon monoxide, 15 mL of THF

and 2 mL of MeOH were added. A 1 M THF solution of 3.31 g (11.1 mmol) of 114b was added and the mixture was stirred for 24 hours at room temperature. The mixture was filtered and concentrated in vacuo. Chromatography on silica gel using hexane/ether (5:1) provided 2.11 g (7.6 mmol, 68%) of 115b (mp 46-47 °C). NMR ($CDCl_3$) 1.32 (t, 3 H, J = 7 Hz), 3.65 (s, 3 H), 3.73 (s, 2 H), 3.83 (s, 3 H), 4.21 (q, 2 H, J = 7 Hz), 6.51 (d, 1 H, J = 16 Hz), 6.80-7.38 (m, 3 H), 7.77 (d, 1 H, J = 16 Hz). IR (film) cm^{-1} 1740, 1715, 1630, 1600, 1575. High resolution mass spectrum for $C_{15}H_{18}O_5$ requires 278.11543; measured 278.11591.

Preparation of 2-Carboxymethyl-6-methoxy Cinnamonitrile (116a)

A solution of 0.69 g (3 mmol) of 115a and 0.63 g (15 mmol) of lithium hydroxide in 15 mL of MeOH was refluxed overnight. The MeOH was evaporated in vacuo and the residue was dissolved in water and acidified. The aqueous mixture was extracted with methylene chloride. The organic solution was washed with brine, dried over Na_2SO_4 and evaporated in vacuo to give 116a (mp 166-168 °C). NMR ($CDCl_3$) 3.70 (s, 2 H), 3.82 (s, 3 H), 6.20 (d, 1 H, J = 17 Hz), 6.70-7.45 (m, 3 H), 7.42 (d, 1 H, J = 17 Hz). IR ($CHCl_3$) cm^{-1} 3400-2300, 2220, 1710, 1615, 1600, 1575. High

resolution mass spectrum for $C_{12}H_{11}NO_3$ requires 217.07390; measured 217.07334.

Preparation of 2-Carboxymethyl-6-methoxy Cinnamic Acid (116b)

A solution of 0.83 g (3 mmol) of 115b and 0.42 g (10 mmol) of lithium hydroxide in 10 mL of MeOH was refluxed overnight. The MeOH was evaporated in vacuo and the residue was dissolved in water and acidified. The aqueous solution was extracted with ethyl acetate. The organic extract was washed with brine, dried over Na_2SO_4 and concentrated in vacuo to provide 116b (mp 177-178 °C). NMR ($CDCl_3/d_6$-acetone) 3.80 (s, 2 H), 3.90 (s, 3 H), 6.53 (d, 1 H, J = 16 Hz), 6.80-7.50 (m, 3 H), 7.80 (d, 1 H, J = 16 Hz). IR (Nujol) cm^{-1} 3400-2200, 1695, 1615, 1590, 1570. High resolution mass spectrum for $C_{12}H_{12}O_5$ requires 236.06848; measured 236.06843.

Preparation of Ethyl 2-Acetoxy-6-methyl Benzoate (119)

One drop of concentrated H_2SO_4 was added to a solution of 1.8 g (10 mmol) of 59 in 6 mL of acetic anhydride. The solution was stirred overnight at room temperature. Most of the anhydride was evaporated in vacuo and the residue was diluted with ether and washed with saturated sodium bicarbonate. The organic solution was washed with brine, dried over Na_2SO_4 and concentrated. The residue was passed through a short column of silica gel to give 2.04 g

(9.2 mmol, 92%) of 119. NMR ($CDCl_3$) 1.33 (t, 3 H, J = 7 Hz), 2.27 (s, 3 H), 2.40 (s, 3 H), 4.35 (q, 2 H, J = 7 Hz), 6.82-7.60 (m, 3 H). IR (film) cm^{-1} 1775, 1725, 1610. High resolution mass spectrum for $C_{12}H_{14}O_4$ requires 222.08921; measured 222.08908.

Preparation of 3-Trimethylsilyloxy-1H-2-benzopyran-1-one (122a)

To a solution of 0.42 mL (3 mmol) of triethyl amine and 0.55 mL (3 mmol) of trimethylsilyltrifluoromethylsulfonate in 7 mL of Et_2O at 0 °C was added 0.24 g (1.5 mmol) of homophthalic anhydride. After the mixture had stirred overnight at room temperature, a two phase mixture had formed. The upper ethereal layer was carefully withdrawn and evaporated to give 122a. Compound 122a rapidly decomposed to homophthalic anhydride on standing in the air. Compound 122a was stable for several hours as a solution in chloroform. NMR ($CDCl_3$) 0.41 (s, 9 H), 5.56 (s, 1 H), 7.05-8.20 (m, 4 H). IR ($CHCl_3$) cm^{-1} 1735, 1650.

Preparation of 3-Methoxy-1H-2-benzopyran-1-one (122b)

To a suspension of 0.16 g (1.0 mmol) of homophthalic anhydride in 5 mL of Et_2O was added an excess of diazomethane (36). The mixture was stirred at room temperature until all of the anhydride had dissolved and gas evolution had ceased. The solution was concentrated in vacuo to give

122b. NMR ($CDCl_3$) 3.90 (s, 3 H), 5.52 (s, 1 H), 7.10-8.15 (m, 4 H). IR ($CHCl_3$) cm^{-1} 1740, 1650. This material has been synthesized by an alternate method (86).

Preparation of 8-Methoxy Homophthalic Anhydride (123)

A solution of 1.9 g (9 mmol) of 6-methoxy homophthalic acid (71) in 40 mL of acetyl chloride was refluxed for 2 hours. The acetyl chloride was evaporated under reduced pressure. The resulting solid was suspended in cold ether and filtered to give 1.56 g (8.1 mmol, 90%) of 123 (mp 148-149 ^{o}C). NMR ($CDCl_3$) 3.98 (s, 3 H), 4.02 (s, 2 H), 6.80-7.72 (m, 3 H). IR ($CHCl_3$) cm^{-1} 1790, 1750, 1590. High resolution mass spectrum for $C_{10}H_8O_4$ requires 192.04226; measured 192.04298.

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