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SYNTHETIC APPROACHES TO THE DEOXYANTHRACYCLINES

Iowa State University PH.D. 1984

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Synthetic approaches to the deoxyanthracyclines

by

Michael Don Hagen

A Dissertation Submitted to the

Graduate Faculty in Partial Fulfillment of the

Requirements for the Degree of

DOCTOR OF PHILOSOPHY

Department: Chemistry
Major: Organic Chemistry

Approved:

Signature was redacted for privacy.

In Charge of Major Work

Signature was redacted for privacy.

For the Major Department

Signature was redacted for privacy.

For the Graduate College

Iowa State University
Ames, Iowa

1984

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INTRODUCTION

During the last 10 years, adriamycin and daunomycin have been major components in the treatment of cancers. However, their toxicity has led to the search for other anthracycline antibiotics. The less toxic 11-deoxyanthracyclines were discovered and have proven to be more effective anticancer drugs than adriamycin and daunomycin. The need to develop new analogues of the anthracyclines still exists; this manuscript will detail the results of a program to develop new analogues by a Diels-Alder/Friedel-Crafts acylation strategy.

HISTORICAL

Since their isolation as highly colored pigments from soil bacteria, the anthracyclines have developed into a large family of naturally occurring compounds. The antitumor properties of the anthracyclines have stimulated this development, which has led to the isolation and synthesis of more clinically effective anthracyclines. Several excellent reviews on the anthracyclines can be found in the literature (1-8).

The name anthracycline is based on the structural features of this family of compounds. They all possess an anthraquinone chromophore within a linear tetracyclic hydrocarbon skeleton. Figure 1 illustrates the basic skeleton and the numbering system of the anthracyclines. They have been isolated as both the glycosides and the aglycones, known as anthracyclinones. The glycoside linkage of the anthracyclines is

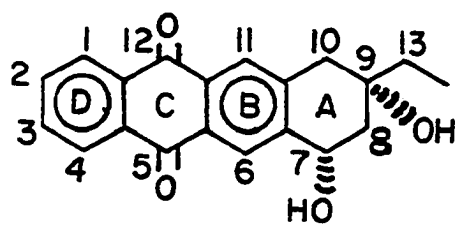
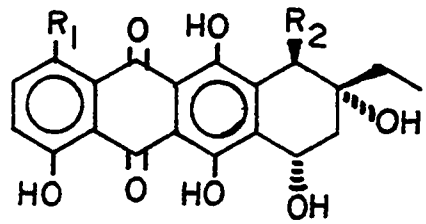
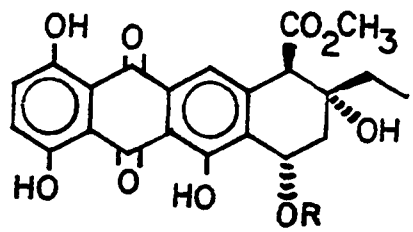


Figure 1. Skeleton and numbering system of the anthracyclines

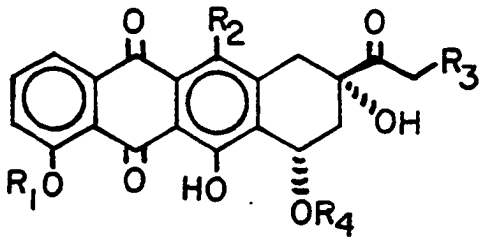
usually between the C-7 hydroxyl and an α-anomer of an L-sugar. Representatives of the anthracyclines and anthracyclinones are shown below.



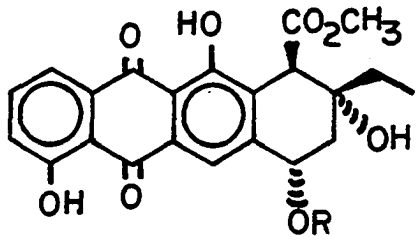
	R_1	R_2
Rhodomycinones	H	CO_2CH_3 or OH
Isorhodomycinones	OH	CO_2CH_3 or OH



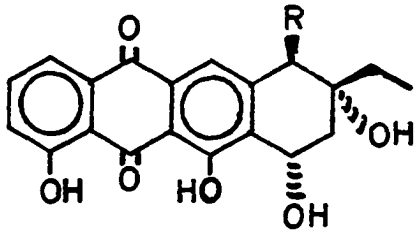
	R
Pyrromycin	Rhodosamine
Cinerubin A	Rhodosamine + 2-deoxy-L-fucose + L-cinerulose
Cinerubin B	Rhodosamine + 2-deoxy-L-fucose + cinerulose B



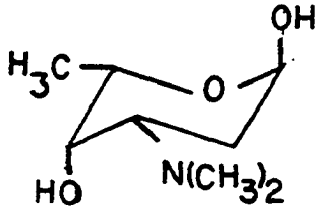
	R_1	R_2	R_3	R_4
Daunomycin	CH_3	OH	H	Daunosamine
11-Deoxydaunomycin	CH_3	H	H	Daunosamine
Adriamycin	CH_3	OH	OH	Daunosamine
11-Deoxyadriamycin	CH_3	H	OH	Daunosamine
Carminomycin	H	OH	H	Daunosamine



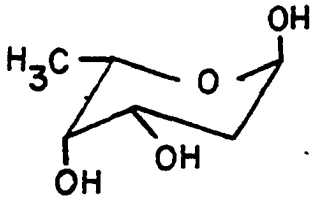
	R
Aklavinone	H
Aclacinomycin A	Rhodosamine + 2-deoxy-L-fucose + L-cinerulose
Aclacinomycin B	Rhodosamine + 2-deoxy-L-fucose + cinerulose B



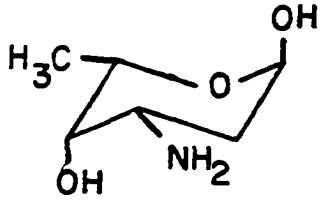
	R
α-Citromycinone	OH
γ-Citromycinone	H



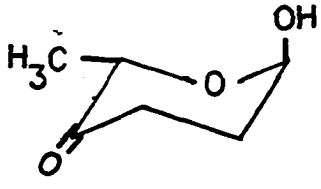
Rhodosamine



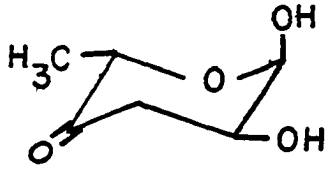
2-Deoxy-L-fucose



Daunosamine



L-Cinerolose



Cinerolose-B

Isolation and Development

The earliest known anthracyclines were isolated by Brockmann and Bauer from Streptomyces purpurascens in 1950 (9a). These anthracyclines were found to possess the aglycones of the rhodomycins and isorhodomycins. These compounds were shown to have potent antibacterial activity and inhibited Ehrlich ascites tumors in mice, but due to their high toxicity there was no increase in survival rates.

Brockmann also reported the isolation of pyrromycin from Streptomyces DOA 125 (9b). Similar compounds were isolated by Ettlinger and coworkers from Streptomyces antibioticus in 1959 (10). These compounds were called cinerubin A and B; they displayed activity against Gram (+) bacteria and certain fungi, cytotoxicity to hen fibroblast cultures, and inhibition of various murine sarcomas and carcinomas. However, their high toxicity in mice and rats prevented further development as antitumor agents.

In 1963, a more selective anthracycline was independently isolated from a mutant strain of Streptomyces peucetius by two groups. Workers at Farmitalia named this compound daunomycin (11a), while workers at Rhone-Poulenc named it rubidomycin (11b). Daunomycin was demonstrated to have potent cytotoxic activity in cell cultures and to inhibit viruses, Ehrlich ascites tumors, and solid tumors; there was also substantial increase in the survival rates of treated animals (12). Although daunomycin is highly toxic, clinical studies were undertaken because of its activity against solid tumors. These studies showed it

had low efficacy in chronic lymphoid leukemias, lymphosarcomas, Hodgekin's disease, and reticulosarcomas, but it could be used for the treatment of acute myeloblastic and lymphoblastic leukemias (13). However, due to its undesirable side effects - which include severe aplasia, immunodepression, and severe cardiotoxicity - daunomycin had limited use.

A more effective drug than daunomycin was isolated from a Streptomyces peucetius strain by Arcamone and coworkers in 1969 (14). This new drug was named adriamycin, also known as doxorubicin. Because adriamycin was found to be less toxic than daunomycin and active against a broader spectrum of tumors (15), adriamycin rapidly replaced daunomycin in clinical trials. Adriamycin was found to be effective against breast and bladder adenocarcinoma, soft tissue and osteogenic sarcomas, bronchogenic and testicular carcinoma, pediatric-solid tumors (Wilms' tumor and Ewing sarcoma), Hodgkin's disease, malignant lymphomas, and acute leukemias (8). Toxic side effects were alopecia, stomatitis, myelosuppression, gastroenteritis, and cardiac toxicity.

Aclacinomycin A and B were isolated from Streptomyces galileus MA144-M1 by Oki and coworkers in 1975 (16). Aclacinomycin A was found to be highly active against L1210 and P388 leukemia, Ehrlich ascites tumors, rat hepatomas, solid tumors, and colon carcinoma. Aclacinomycin A showed favorable response in patients with acute leukemias (which were refractory to daunomycin and adriamycin), malignant lymphoma, and lung, breast, ovarian, stomach, and urinary bladder cancers when

administered by intravenous infusion (7). Aclacinomycin A was also moderately or weakly active against other cancers (4) and was found to be approximately 10 times less cardiotoxic than adriamycin in hamsters and rabbits (17).

More recently, Arcamone and coworkers isolated several 11-deoxy-anthracyclines, including 11-deoxydaunomycin and 11-deoxyadriamycin, from a Micromonospora peucetica strain (18). When tested in vivo on P388 leukemia, they were found to be just as active as adriamycin at 10 times the dosage. Toxicity studies have yet to be reported.

Biosynthesis

The biosynthesis of the anthracyclines arises from the consecutive "head to tail" condensation of 9 acetates and 1 propionate to produce the hypothetical polyketide 1 (see Figure 2). This incorporation of 9 acetates and 1 propionate has been proven from labeling studies with mutated strains of Streptomyces (19). The tetracyclic ring system 2 is formed via aldol condensations with concomitant loss of water. The chrysazinanthranol derivative 3 can then be produced by reduction of the C-2 and C-7 carbonyls, elimination of the C-2 hydroxyl, and enolization. Intermediate 3 is then oxidized to aklavinone 4, which is the precursor for other anthracyclines (7). Daunomycinone is formed by a series of oxidations and a decarboxylation, while hydroxylations at C-1 and/or C-11 produces ε-rhodomycinone 5 and ε-pyrromycinone 6 (8).

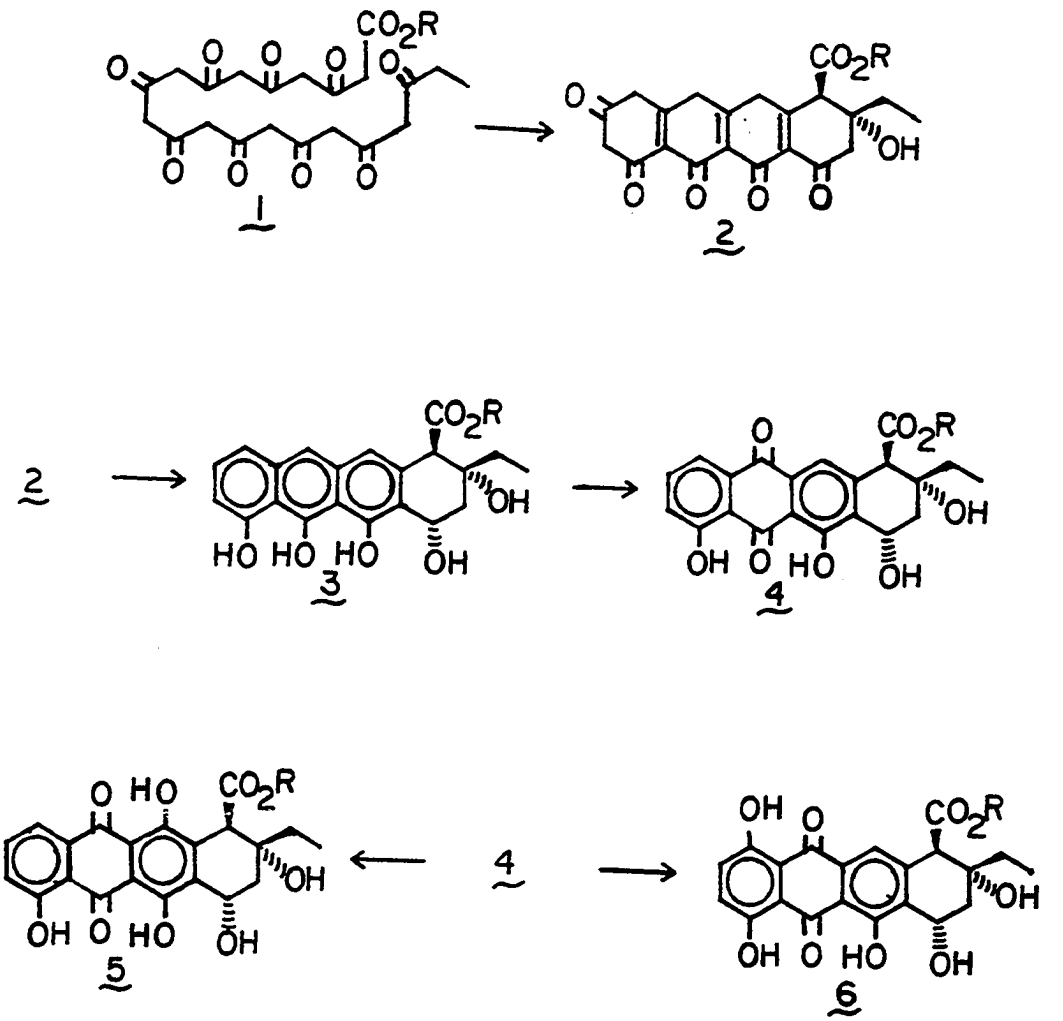


Figure 2. Biosynthesis of the anthracyclines

Mechanism of Action

Researchers have also studied the mechanism of action of the anthracyclines. Their antitumor activity is due to binding interactions between the drug and deoxyribonucleic acid (DNA). When double-stranded DNA and anthracyclines are mixed in solution, there are noticeable changes in the physical and spectral properties of these compounds (20). The anthracycline's ultraviolet, visible, fluorescence, and polarographic properties are changed, while the sedimentation rate, viscosity, and denaturation profile of the DNA are also changed. This information and data from X-ray diffraction studies of anthracycline-DNA complexes (21) indicate that the anthracycline intercalates between the base pairs of the DNA helix.

The X-ray analysis of N-bromoacetyldaunomycin, along with NMR analyses, have shown that the A ring exists in a half chair conformation (22). This conformation is stabilized by the intramolecular hydrogen bonding between the C-7 oxygen and the C-9 hydroxyl hydrogen (Figure 3).

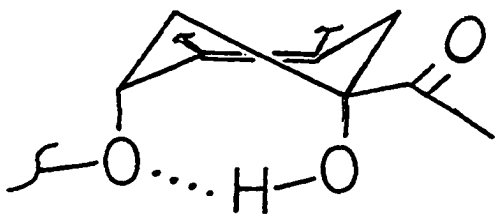


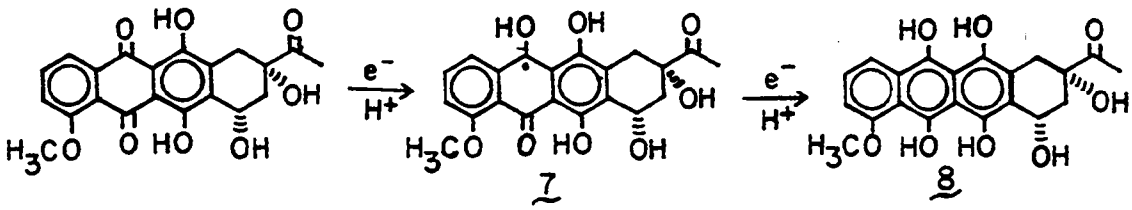
Figure 3. Conformation of the A ring

With this information and the previous data, a detailed model for the binding interaction can be proposed. The major binding force is the extensive overlap between the planar anthraquinone chromophore of the anthracycline and the two adjacent base pairs of the DNA, which are immediately above and below the planar chromophore. Stabilization of this interaction is due to a variety of ionic and hydrogen bonding interactions between the electron-deficient quinone chromophore and the electron-rich purine and pyrimidine bases (8). Also, additional stabilization can occur by the ionic interactions of the anthracycline's amino sugar moiety (which is in the major groove of the DNA helix) and the phosphates of the DNA. These interactions occur between the protonated amino group of the sugar and the second phosphate from the intercalation site. Hydrogen bonding between the C-9 hydroxyl and the first phosphate from the intercalation site is also possible.

The direct consequence of this intercalation is the inhibition on the template activity of the DNA, thus causing the death of the cancer cell. However, the detailed mechanism of this inhibition remains to be established; both preventing the separation of the DNA strands and hindering the attachment of the polymerase (due to the distortion of the DNA structure) have been suggested as possible causes for this inhibition of DNA synthesis (23).

However, this intercalation of DNA cannot account for the breakage of DNA strands, breakage which has been observed *in vivo* and *in vitro*. Kleyer and Koch have recently reported that the reduction of

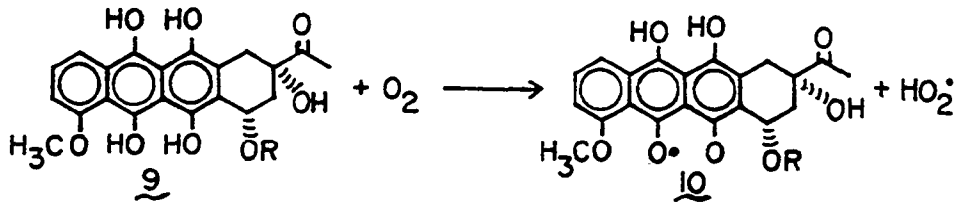
daunomycinone to hydroquinone 8 occurs via two sequential one-electron reductions (24). Previous evidence indicates that the enzyme NADPH, which is present in the microsomes of cells, catalyzes this reduction



of the quinone chromophore to produce the semiquinone 7 (25). Sato and coworkers have shown that semiquinone 7 forms in vitro and that no radicals are formed by the drug-DNA complex with NADPH (26). Thus, semiquinone 7 must be formed before intercalation of the DNA occurs. In the presence of molecular oxygen, semiquinone 7 acts as an electron shuttle by producing superoxide radicals; by intercalating into the DNA helix, superoxide can be generated in proximity of the DNA strands causing the damage to the strands (25).

Lown and coworkers have reported that no cleavage of DNA occurred with the addition of anthracyclines, but when an anthracycline/DNA mixture was treated with a reducing agent ($NaBH_4$), cleavage was observed at a slow rate (27). Rapid cleavage was observed when hydroquinone 9 was added to a DNA solution, thus indicating that the intercalated quinone chromophore is shielded from the reducing agent. They also reported that less cleavage occurred with the reduced aglycones, revealing the importance of the amino sugar-DNA interactions. Oxidation

of hydroquinone 9 by molecular oxygen could generate superoxide and peroxide (Figure 4), which can then damage the DNA strands. This



$$HO_2\cdot \longrightarrow H^+ + O_2^{-\cdot}$$

$$2O_2^{-\cdot} + 2H^+ \longrightarrow H_2O_2 + O_2$$

$$H_2O_2 + O_2^{-\cdot} \longrightarrow HO\cdot + HO^- + O_2$$

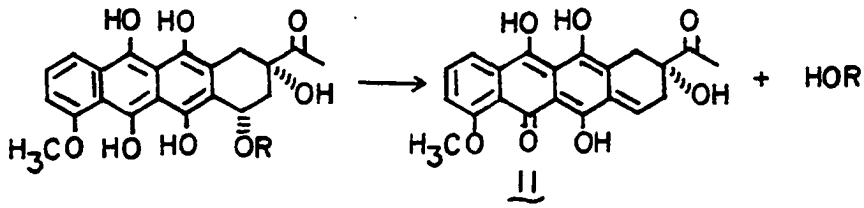
$$HO\cdot + DNA \longrightarrow \text{damaged DNA}$$

Figure 4. Generation of superoxide and peroxide

mechanism also accounts for the cardiotoxicity of the anthracyclines. Since heart tissue has low levels of catalase and superoxide dismutase, Nohl and Jordan have suggested that the cardiotoxicity is due to the generation of the hydroxide radical and not superoxide (28).

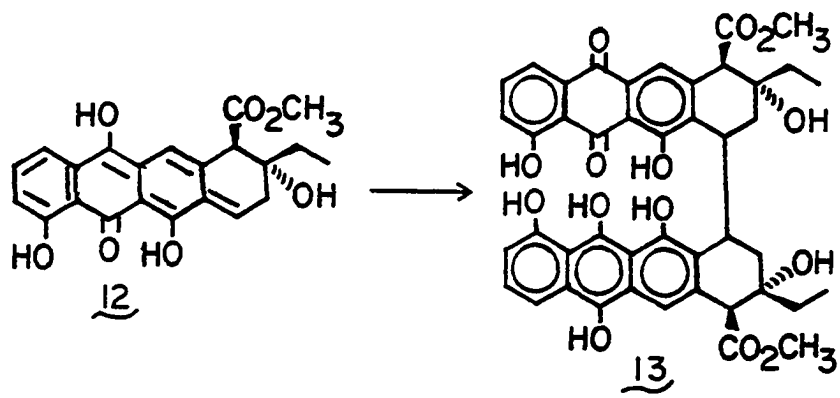
In the absence of molecular oxygen, reduction of anthracyclines results in the formation of the 7-deoxyanthracyclines (29) and covalent binding of the drug to cellular macromolecules (30) via a semiquinone intermediate. This covalent binding has also been suggested to occur from the hydroquinone intermediate via a quinone methide (31). The existence of quinone methide 11 has been demonstrated from kinetic and

spectroscopic studies (32). Furthermore, quinone methide 11 has been trapped by benzaldehyde (33) and by thiol and thiolate nucleophiles (34). Thus, quinone methide 11 can react with either electrophilic



11

or nucleophilic sites of the DNA. Kinetic and spectroscopic studies on aclacinomycin A suggest that reductive elimination of the glycoside forms quinone methide 12, which can be protonated or dimerize to dimer



13 (35). The absence of the 11-hydroxy in quinone methide 12 makes it less basic and nucleophilic and more electrophilic than quinone methide 11. These differences result in the formation of dimer 13 and may be responsible for their differences in biological activity. By binding

to the DNA, the anthracycline can prevent DNA synthesis and generate reactive oxygen species in the proximity of the DNA strands.

Structure-Activity Relationships

The outstanding cancer chemotherapeutic efficacy of adriamycin has stimulated the search for anthracyclines that do not exhibit the severe and cumulative dose-dependent cardiotoxicity of adriamycin. This search has led to the clinically effective aclacinomycin A by Oki and coworkers. By the use of microbial and chemical glycosidation, modification, and isolation, the relationships between structure and activity of over 61 anthracyclines have been studied (7). A brief summary of these relationships is outlined below:

1. The amino group of the sugar moiety is essential for activity.
2. Anthracyclines with di- or trisaccharides are more potent *in vitro* than the monosaccharide compounds.
3. Hydroxyls at C-1, C-2, C-4, C-6, and C-11 influence the *in vitro* and *in vivo* activity.
    a) Compounds without the C-6 hydroxyl group have lower cytotoxicity and inhibitory effect on RNA and DNA synthesis than those with the C-6 hydroxyl.
    b) Replacement of C-4 or C-6 hydroxyl with a methoxyl decreases the potency of the drug.
    c) Hydrophobicity at C-4 and *in vitro* potency increase in parallel: CH_3O < HO < H.

d) Hydroxyls at C-1 and/or C-11 increase the potency but decrease the antitumor activity due to their toxicity.

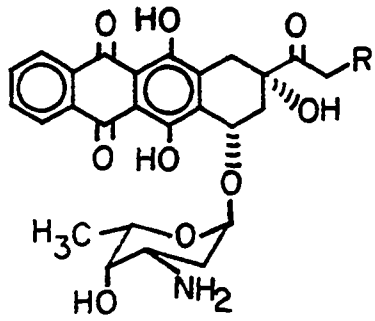
4. The C-10 methoxycarbonyl with R-configuration is important in the inhibition of RNA synthesis.
5. The length of C-9 side chain has a slight influence on cytotoxicity and inhibition of RNA and DNA synthesis.

DiMarco and coworkers have reported that methylation of the C-6 and C-11 hydroxyls of daunomycin results in complete loss of bioactivity and affinity for DNA (36). Methylation of the C-6 or C-11 hydroxyl of 4-O-demethyldaunomycin did not destroy its bioactivity, thus indicating the importance of a chelated quinone chromophore.

The length of the saccharide is important in inhibiting DNA and RNA synthesis (37). Anthracyclines with a monosaccharide chain inhibit DNA and RNA synthesis at approximately equivalent concentrations. However, anthracyclines with a polysaccharide chain inhibit RNA synthesis at lower concentrations than those needed for DNA inhibition. The inhibition of RNA synthesis at lower concentrations is due to the polysaccharide occupying the major or minor groove of the DNA helix, thus interfering with the movement of RNA polymerase (38). The polysaccharide can also decrease the DNA inhibition by decreasing the binding of the drug to the DNA.

Synthetic Approaches

Both 4-demethoxydaunomycin 14 and 4-demethoxyadriamycin 15 have been synthesized, and their properties have been studied (8). While



14 R=H
15 R=OH

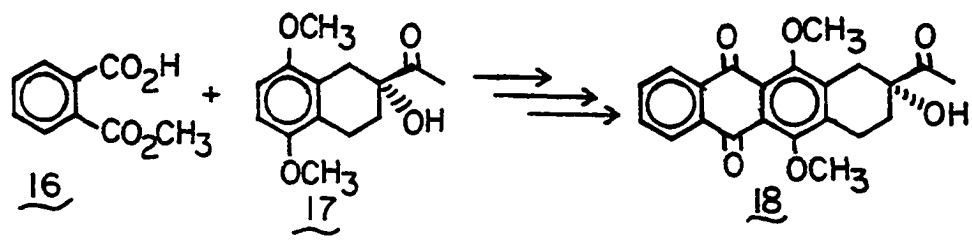
4-demethoxydaunomycin was found to be 8 times more active than daunomycin, it was also more toxic than daunomycin. The 4-demethoxy-adriamycin was found to be more effective at lower doses than adriamycin and was also found to be orally active.

Because of these findings and the previously given structure-activity relationships, synthetic chemists have begun to synthesize the deoxyanthracyclines in hopes of developing new anthracyclines with diminished toxicity, improved activity, and facile preparation.

Any synthetic approach to the deoxyanthracyclines must overcome two synthetic problems. These problems are regioselective formation of the linear tetracyclic skeleton and introduction of the C-7 hydroxyl. The latter problem is usually accomplished via a benzylic bromination/

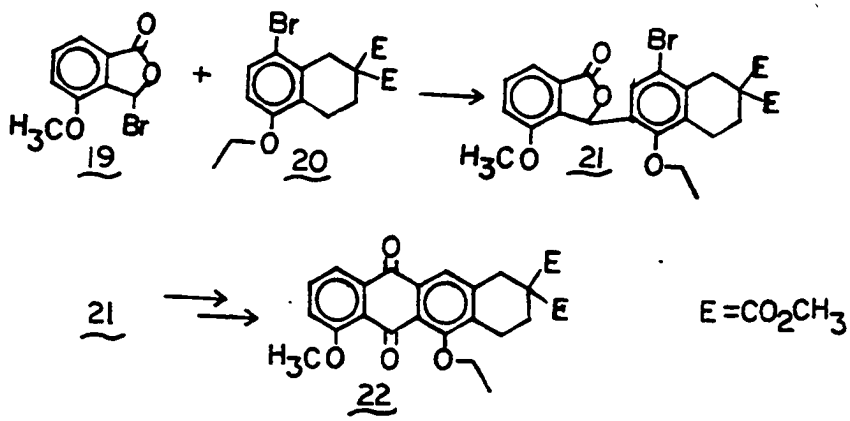
solvolysis sequence. However, the efficiency of this sequence varies from excellent for the 11-deoxyanthracyclines to poor for the 6-deoxy-anthracyclines and daunomycin series. The formation of the tetracyclic skeleton of the deoxyanthracyclines can be divided into several strategies: Friedel-Crafts acylation and alkylation, cycloadditions, and anionic approaches. A brief summary of previous synthetic efforts towards the deoxyanthracyclines involving these strategies will be given.

The Friedel-Crafts reaction has played an important role in the synthesis of the deoxyanthracyclines. Wong and coworkers have used an AB + D strategy in their synthesis of 4-demethoxydaunomycinone (39). Their synthesis involved the acylation of tetralin 17 with the phthalic acid monomethyl ester 16, alkaline hydrolysis, and subsequent cyclization to afford anthraquinone 18 in a 23% yield. This intermediate was then transformed into 4-demethoxydaunomycinone in several steps. Several similar syntheses of 4-demethoxydaunomycinone have been reported (40).

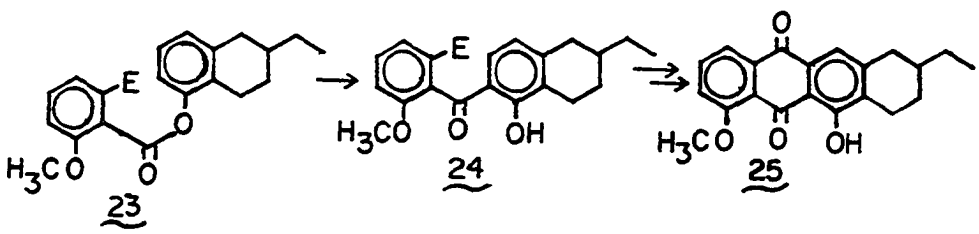


Johnson and coworkers have utilized a convergent Freidel-Crafts alkylation strategy in their synthesis of 11-deoxydaunomycinone (41). Alkylation of tetralin 20 with bromophthalide 19 produced phthalide 21

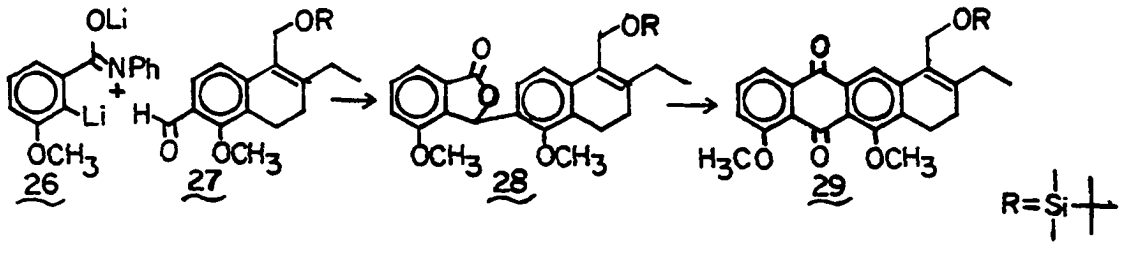
(with complete control of regiochemistry) in 86% yield. Transformation of phthalide 21 to anthraquinone 22 was accomplished in excellent yields via hydrogenolysis, cyclization, and oxidation. Anthraquinone 22 was then successfully converted to 11-deoxydaunomycinone. Rama Rao and coworkers have reported a similar synthesis (42).



Confalone and Pizzolato have synthesized aklavinone by the use of the Fries rearrangement (43). Aryl ester 23, which was prepared from the corresponding tetrahydronaphthol and methoxy phthalic acid monomethyl ester, gave exclusively the o-hydroxybenzophenone 24 in 73% yield at 120°C. At lower temperatures, a mixture of ortho/para isomers was obtained. Saponification and cyclization produced anthraquinone 25 in 57% yield which was subsequently transformed into alkavinone; however, the overall yield for this synthesis is extremely poor. A similar strategy has been used for the formation of a 11-deoxydaunomycinone intermediate (44).

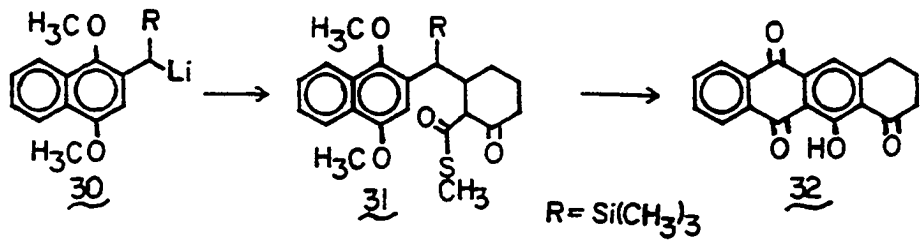


Aklavinone has also been synthesized by Kende and Rizzi via an AB + D strategy (45). Addition of aldehyde 27 to the metallated carboxamide 26 followed by cold acidic workup gave phthalide 28 in 80% yield. Phthalide 28 was converted into anthraquinone 29 via hydrogenolysis, cyclization, and oxidation in an overall yield of 56%. Functionalization of the A ring resulted in a stereospecific and enantioselective synthesis of aklavinone in an overall yield of 6.5%. Decarbomethoxyaklavinone (46) and 11-deoxycarminomycinone (47) have also been synthesized by this strategy.

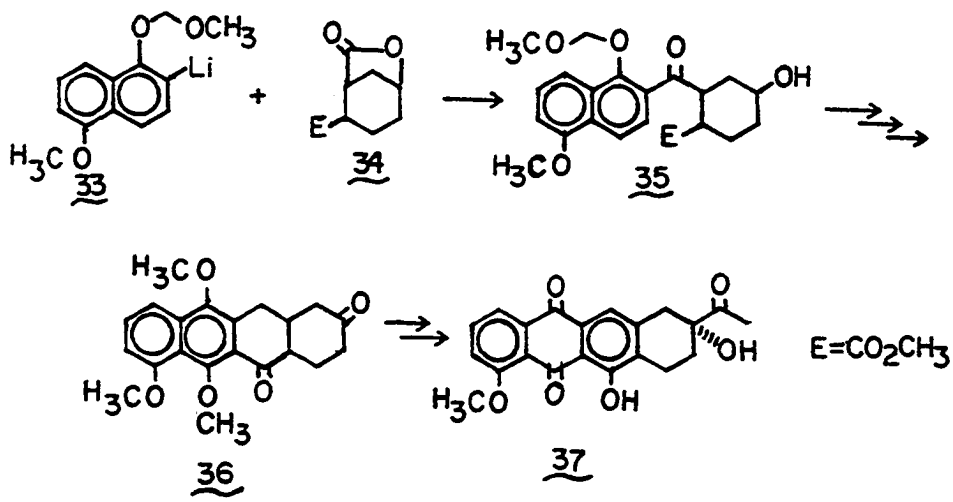


Vedejs and Nader have used an A + CD strategy in their synthesis of a 4-demethoxy-11-deoxyanthracycline intermediate, which possess the necessary oxygenation at C-7 (48). A 1,4-addition of benzyl anion

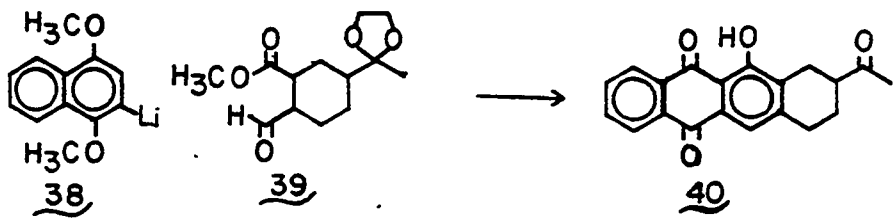
30 to cyclohexenone and subsequent trapping of the resulting enolate gave thioester 31 in 66% yield. Cyclization of thioester 31 with cuprous triflate and oxidation with silver (II) oxide produced anthraquinone 32 in 56% yield. Thioester 31 is an ideal enolate carboxylation product because it can be cyclized without activation.



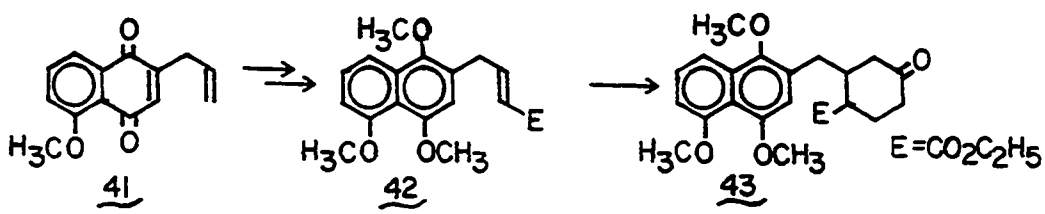
Another A + CD approach to the 11-deoxyanthracyclines involved the addition of lactone 34 to the metallated naphthalene 33 to produce ketoester 35 in 73% yield (49). Ketoester 35 was converted to tetracyclic diketone 36 in 8 steps (27% yield). Anthraquinone 37 was obtained in 29% yield from tetracyclic diketone 36 in 6 steps.



Penco and coworkers have used a similar approach in their synthesis of 4-demethoxy-6-deoxydaunomycinone (50). Their route was extremely short (10 steps), but the formation of anthraquinone 40 from naphthalene 38 and aldoester 39 was extremely poor (10% yield).

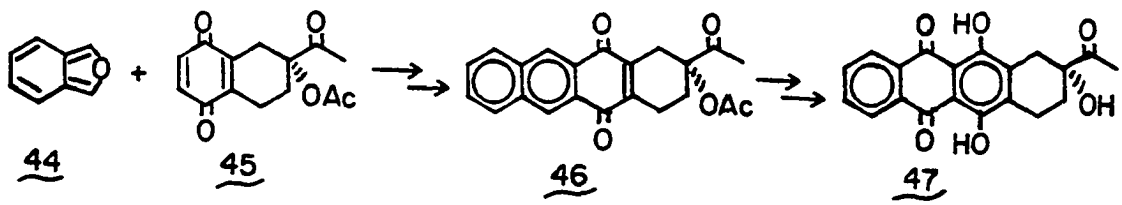


Tetracyclic diketone 36 has also been prepared by Rama Rao and coworkers (51). Cycloaddition of 2-methoxy-1,3-butadiene with α,β-unsaturated ester 42 (produced in a 20% yield from naphthoquinone 41) followed by acidic hydrolysis gave ketoester 43 in 60% yield. Saponification and cyclization produced tetracyclic diketone 36 in excellent yield. A similar strategy was used in the synthesis of 4-demethoxydaunomycinone (52).



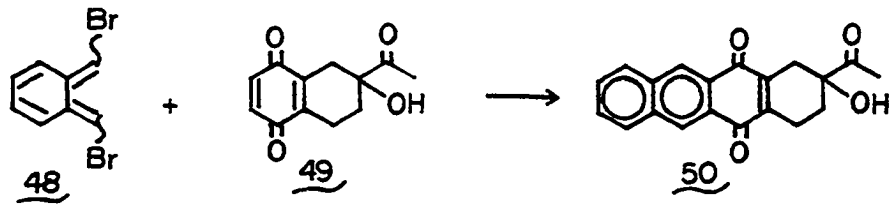
The application of the Diels-Alder reaction to build up the tetracyclic ring system of the deoxyanthracyclines has been widely explored and represents one of the most attractive and versatile approaches. As in the case of the Friedel-Crafts approaches, the

tetracyclic skeleton of the deoxyanthracyclines can be formed via the AB + D strategy. Kende and coworkers have used this strategy in their synthesis of 4-demethoxydaunomycinone (53). Cycloaddition of isobenzofuran 44 (generated in situ) with tetrahydronaphthoquinone 45 and subsequent aromatization produced tetracyclic quinone 46 in 67% yield. Anthraquinone 47 was synthesized in 40% yield from quinone 46 via reductive acetylation of the quinone, oxidation of the C ring, and hydrolysis of the acetates. A benzylic bromination/solvolysis sequence produced the desired product in a moderate yield.



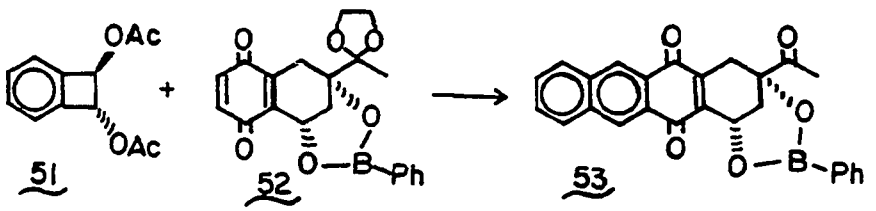
44 45 46 47

Anthraquinone 47 has also been constructed by Wiseman and coworkers (54). Their route is very similar to the previous one and involves the trapping of o-quinodimethide 48, which is generated in situ from the tetrabromide, with tetrahydronaphthoquinone 49. However, tetracyclic quinone 50 was produced in only 33% yield.



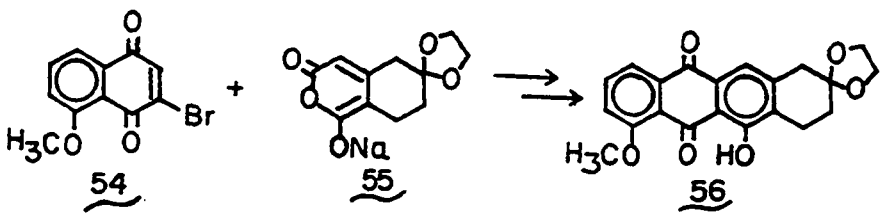
48 49 50

Another route to 4-demethoxydaunomycinone via o-quinodimethides has also been reported (55). Trapping of the o-quinodimethide generated from the thermal ring opening of benzocyclobutene 51 with tetrahydronaphthoquinone 52 produced tetracyclic quinone 53 in 79% yield. This synthesis of 4-demethoxydaunomycinone solves the problems associated with the introduction of the C-7 hydroxyl and is accomplished in a good overall yield. These are the only examples of the AB + D strategy.



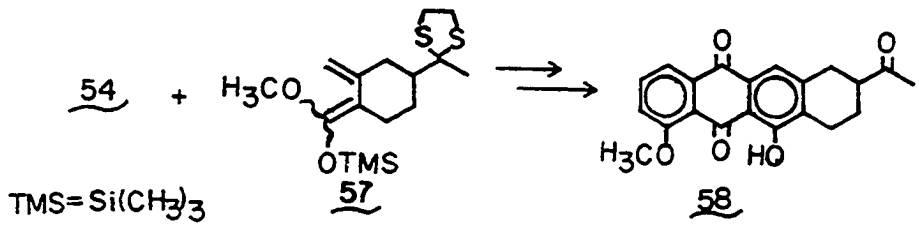
51 52 53

However, the A + CD strategy has received more attention from synthetic chemists. Tamura and coworkers have prepared the 11-deoxycarminomycinone intermediate 56 by the cycloaddition of diene 55 and O-methyl-3-bromojuglone 54 with excellent control of the regiochemistry and in 78% yield (56). A similar route has been reported by Jung and coworkers (57).

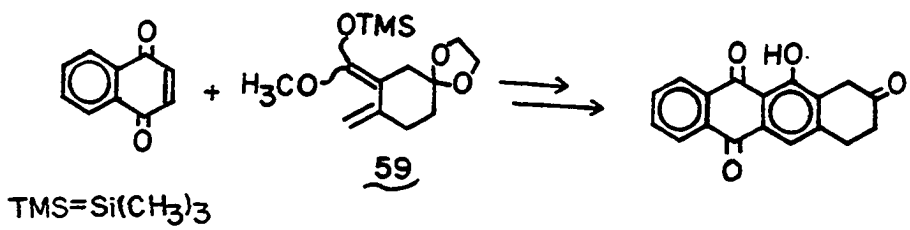


54 55 56

The cycloaddition of vinyl ketene acetals (A ring synthons) with naphthoquinones has been shown to produce tetracyclic intermediates with control of regiochemistry and in moderate yields (58). Gesson and Mondon have extended this work in their synthesis of 11-deoxydaunomycinone

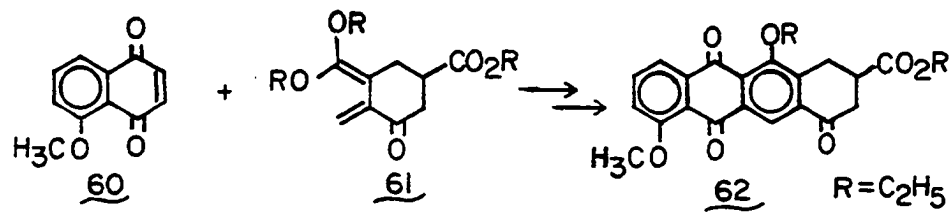


(59). Cycloaddition of vinyl ketene acetal 57 with O-methyl-3-bromojuglone 54 and subsequent deketalization produced anthraquinone 58 in 71% yield. However, conversion of anthraquinone 58 to 11-deoxydaunomycinone was accomplished in a poor overall yield. Gesson and coworkers have also constructed 6-deoxyanthracycline intermediates in moderate yields via vinyl ketene acetal 59 (60).

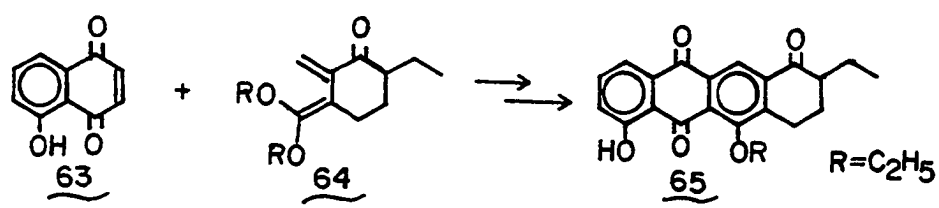


Vinyl ketene acetals generated by the thermolysis of cyclobutenes have also been used for the construction of the deoxyanthracycline skeleton. Both 6-deoxydaunomycinone and 6-deoxyadriamycinone have been synthesized from anthraquinone 62 (61). However, anthraquinone 62 was

prepared in a 4:1 mixture of regioisomers (93% yield) from vinyl ketene acetal 61, which was generated in situ from the corresponding cyclobutene, and O-methyljuglone 60.

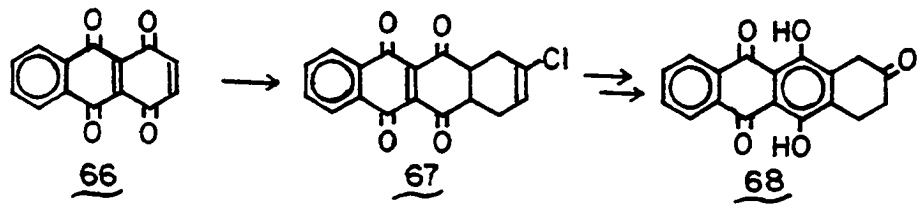


Boeckman and Sum have also used this approach in their synthesis of aklavinone (62). Cycloaddition of the thermally generated vinyl ketene acetal 64 with juglone 63 produced the anthraquinone 65. As in the previous example, a mixture of regioisomers was formed.

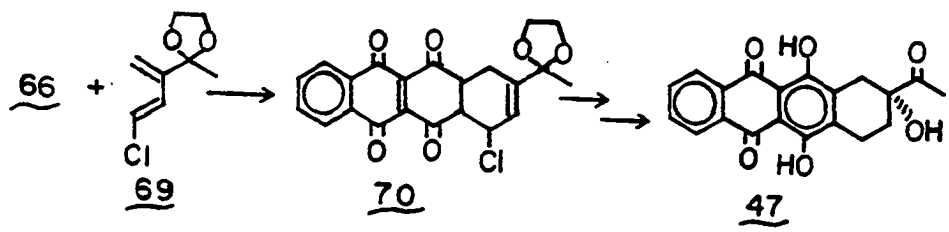


An additional approach using the cycloaddition strategy utilizes a BCD ring intermediate. Kimura and coworkers have recently reported an extremely short and efficient synthesis of a 4-demethoxydaunomycinone intermediate based on this approach (63). The cycloaddition of 2-chloro-1,3-butadiene with quinizarin quinone 66 (prepared in 58% yield from quinizarin) produced the tetraketone 67 in excellent yield. This cycloaddition takes advantage of the subtle differences in

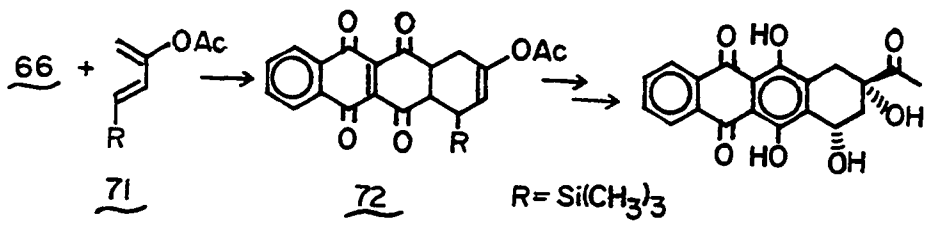
reactivity of the internal double bond versus the external double bond of quinone 66 with electron poor dienes (64). The conversion of tetraketone 67 to anthraquinone 68 was accomplished in 89% yield via aromatization of the B ring and hydrolysis of the vinyl chloride.



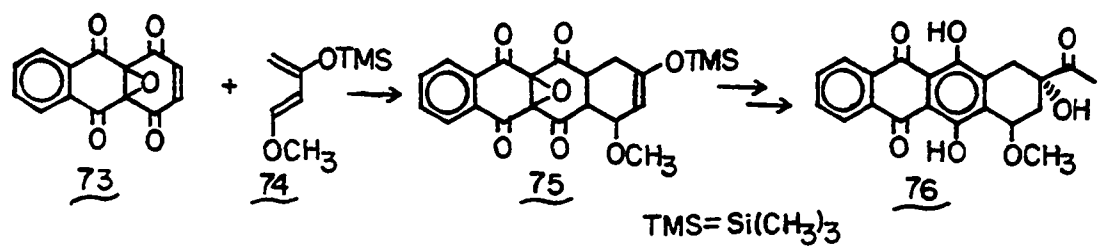
Similar syntheses of 4-demethoxydaunomycinone have been reported. Kelly and Tsang have prepared the tetraketone 70 in excellent yield from quinone 66 and diene 69 (65). Tetraketone 70 was converted to



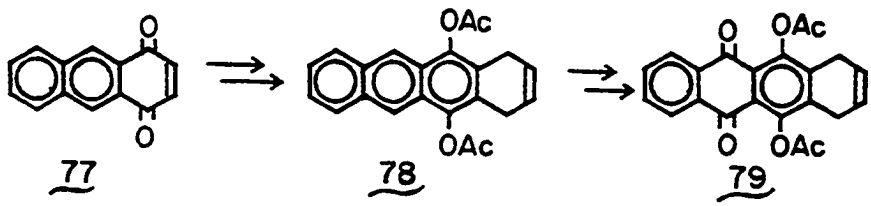
anthraquinone 47 in 5 steps (40% yield). Garland and coworkers have prepared tetraketone 72 from diene 71 in a 77% yield (66). This synthesis has a distinct advantage over the previous two in that the C-7 hydroxyl is introduced in excellent yield via the benzylic trimethylsilyl group.



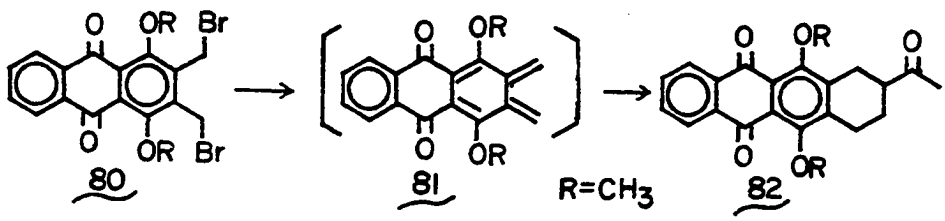
Several approaches to solve the problem of internal addition of electron rich dienes to quinone 66 have been reported. Epoxidation of quinone 66 produces oxirane 73, which forces cycloaddition to occur at the external double bond (67). Using this strategy, Jackson and Stoodley prepared tetraketone 75 in 70% yield from oxirane 73 and diene 74 (68). Tetraketone 75 was smoothly converted to the 4-demethoxy-



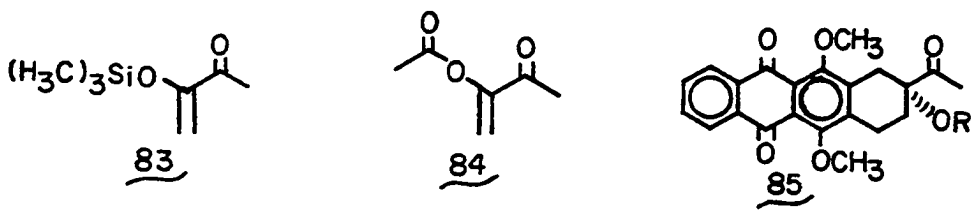
daunomycinone derivative 76. Alternatively, quinizarin can be reduced to the tricyclic quinone 77 in excellent yield (69). Cycloaddition of quinone 77 with 1,3-butadiene, followed by aromatization and acetylation, produced anthracene 78 in 68% yield. Bromination, oxidation, and debromination of anthracene 78 gave anthraquinone 79, which was easily transformed into anthraquinone 68.



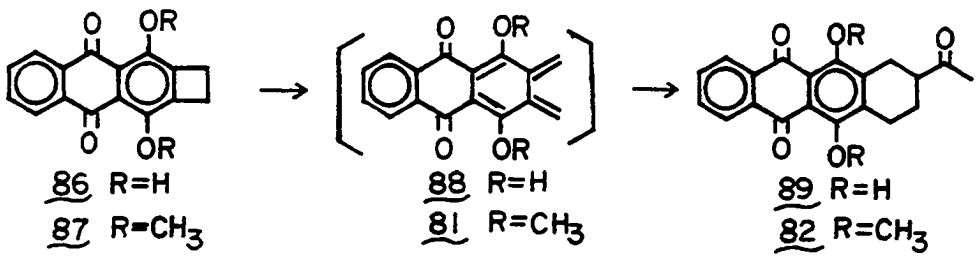
The use of o-quinodimethides as BCD ring intermediates has also been reported. Cava and coworkers have trapped o-quinodimethide 81 (generated from anthraquinone 80) with methyl vinyl ketone to produce anthraquinone 82 in moderate yields (70). The anthraquinone 80 can be readily prepared from quinizarin. Anthraquinone 82 was then



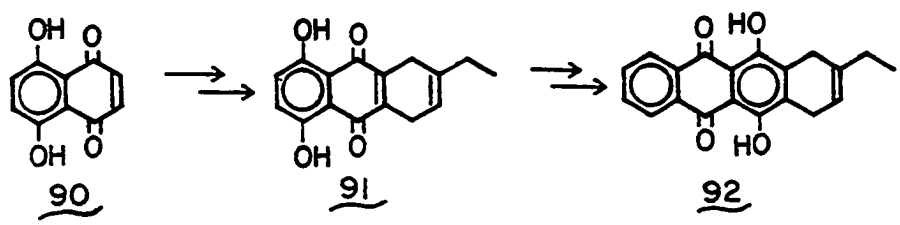
elaborated to anthraquinone 47 in 3 steps and has also been used in an asymmetric synthesis of 4-demethoxydaunomycinone (71). Also, o-quinodimethide 81 has been trapped with dienophile 83 in 12% yield and dienophile 84 in 46% yield to give the C-9 oxygenated anthraquinone 85 (72).



The generation of o-quinodimethides from the thermal ring opening of benzocyclobutenes 86 and 87 has also been reported (73). This route is an improvement on the previous route because it occurs in higher yields, uses a smaller ratio of diene to dienophile, and has wider applications.

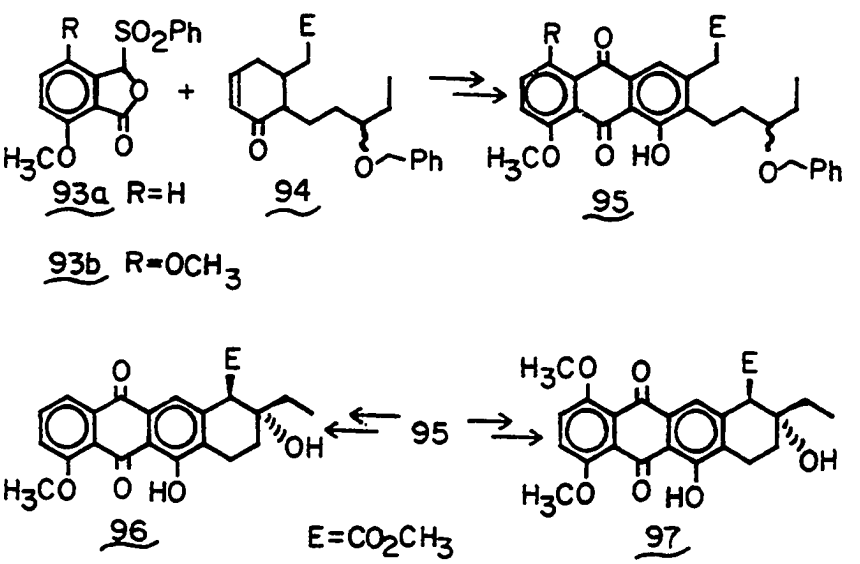


Naphthazarin 90 has been used as an effective starting material for the construction of tetracyclic skeletons (74). Krohn and Rosner have synthesized 4-deoxy-γ-rhodomycinone from naphthazarin in an excellent overall yield (74a). Their synthesis involved the formation of tricyclic quinone 91, which can undergo a second cycloaddition (via its tautomer) to produce the tetracyclic quinone 92. A similar approach was used to synthesize 4-demethoxydaunomycinone (74b).



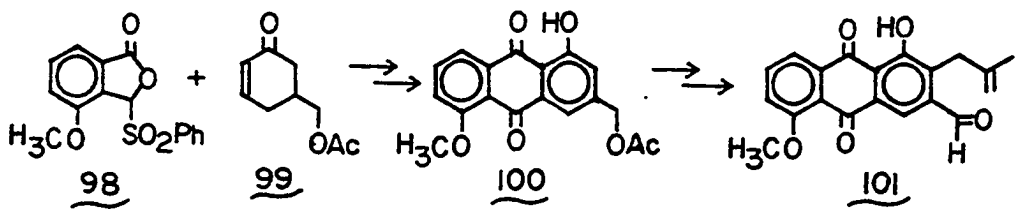
Several other examples of constructing the carbon skeleton of the deoxyanthracyclines via the cycloaddition strategy have been reported (75).

The last strategy to be summarized is the anionic approach. Hauser and coworkers have developed a phthalide sulfone annelation strategy, which is convergent, efficient, and regiospecific (76). Recently, Hauser and Mal have reported the synthesis of aklavinone and ε-pyrromycinone from phthalide sulfones 93a and 93b, respectfully (77). Condensation of enone 94 with the phthalide sulfones 93 produced the



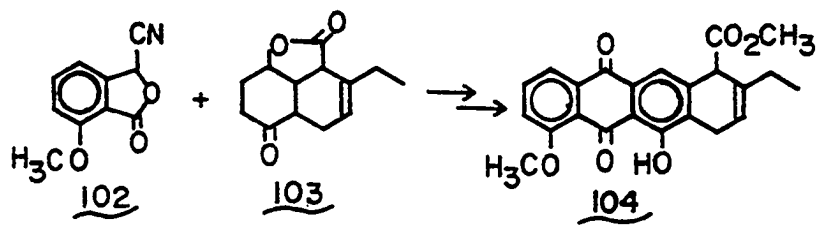
anthraquinones 95 in excellent yield. Formation of the A ring was accomplished via an intramolecular aldol cyclization. In both cases, the major product was the desired isomers 96 and 97. This strategy was also used for the synthesis of γ-citromycinone (78). Condensation

of enone 99 with phthalide sulfone 98 produced anthraquinone 100; however, the yield was only 55%. The A ring was formed by a Claisen rearrangement and subsequent cyclization of anthraquinone 101 with tin tetrachloride.



98 99 100 101

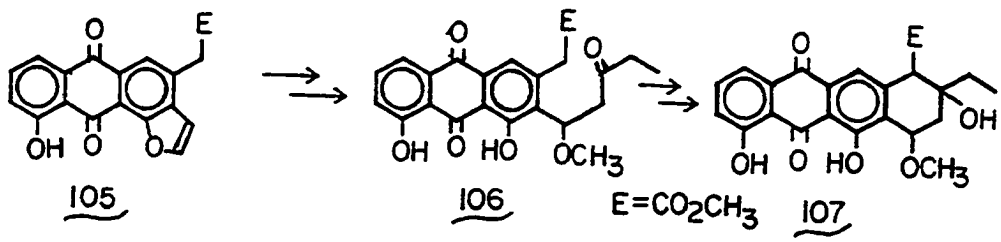
Aklavinone has also been prepared by the use of a cyanophthalide (79). The anthraquinone 104 was formed from the addition of cyanophthalide 102 to enone 103 and subsequent air oxidation and esterification; the overall yield for this transformation was 42%.



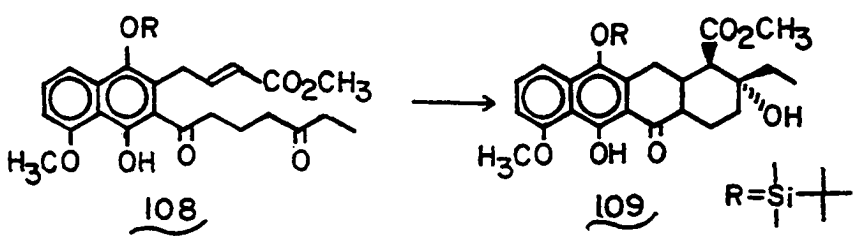
102 103 104

Intramolecular cyclization of an anthraquinone intermediate has been an important strategy in the synthesis of deoxyanthracycline intermediates (80). One of the first syntheses of aklavinone was accomplished by this approach (81). Anthraquinone 106 was prepared from benzofuran 105 in 70% yield via ozonolysis and aldol condensation. Intramolecular cyclization of anthraquinone 106 produced a mixture of

aldol products 107. However, this mixture could be equilibrated. Thus, the overall yield of aklavinone from 2-bromojuglone (precursor to benzofuran 105) was 37% with the equilibrations. This work has been extended to include the asymmetric syntheses of aklavinone (82) and 11-deoxydaunomycinone (83).

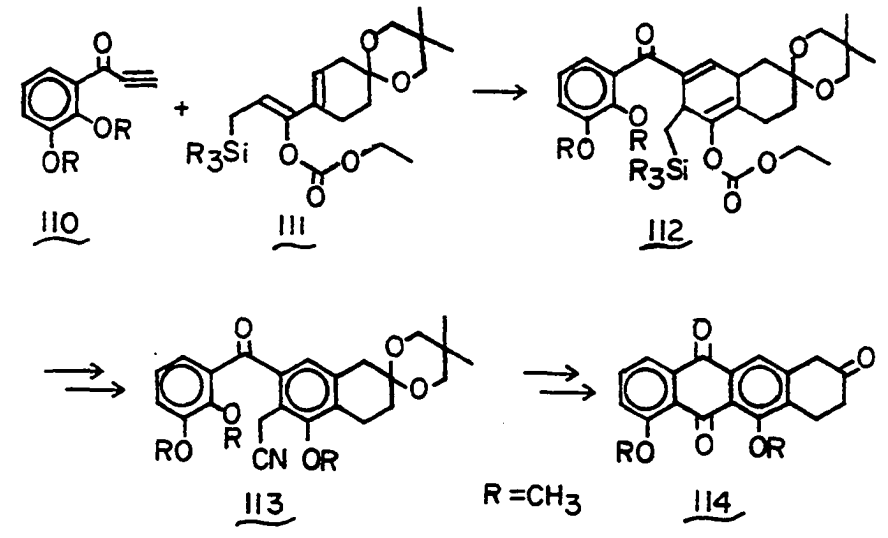


A similar approach was used by Maruyama and coworkers in their synthesis of aklavinone (84); however, both the A and B rings were formed via the intramolecular cyclization of naphthalene 108. As in the previous case, a mixture of products was obtained with the desired tetracyclic ketone 109 isolated in a 53% yield.

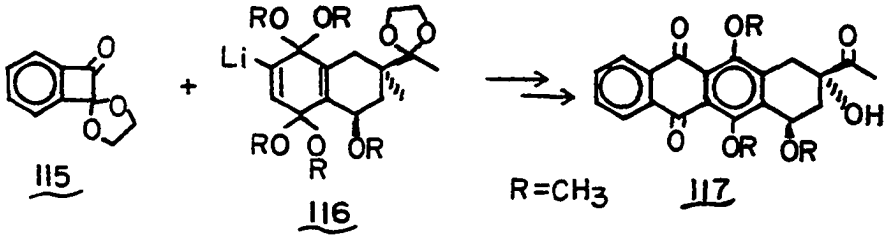


Vedejs and coworkers have reported a silicon mediated approach to the 11-deoxyanthracyclines (85). Cycloaddition of ketoacetylene 110 and diene 111 gave adduct 112 in 86% yield and the isomeric adduct in

8% yield. Adduct 112 was then transformed into the benzyl cyanide 113 in 5 steps. Hassall cyclization, oxidation, and deketalization produced anthraquinone 114 in a good overall yield.

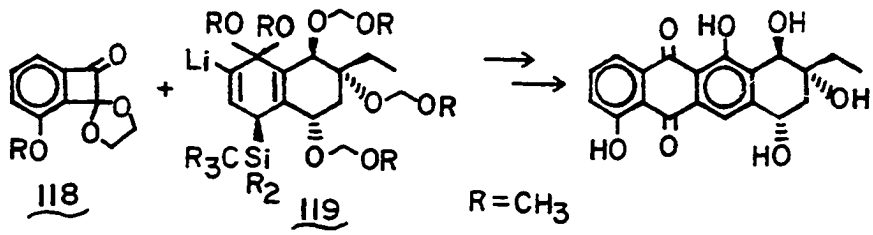


The last anionic approach is the 1,4-addition of metallated quinone bisketals to benzocyclobutenones. Using this approach, Swenton and coworkers have prepared 4-demethoxydaunomycinone from anthraquinone 117, which was prepared by the addition of benzocyclobutenone 115 to the lithiated quinone bisketal 116 in 62% yield (86). This strategy



has also been used to synthesize α-citromycinone via the addition of benzocyclobutenone 118 to the lithiated p-quinol synthon 119 (87).

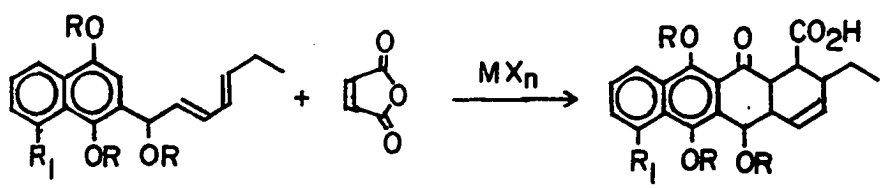
Although this strategy allows the use of a functionalized A ring intermediate and occurs regioselectively, the overall yields are relatively low.



In conclusion, the anthracyclines are an important class of anti-tumor antibiotics which have proven successful in clinical trials. However, their cardiotoxicity has been a major drawback of these drugs. Thus, chemists have developed analogues which are both more therapeutic and less toxic. The synthetic approaches to these analogues are varied and include the Friedel-Crafts acylation and alkylation, cycloadditions, and anionic approaches; overall, these strategies have been used effectively to produce these analogues, but improvements to these strategies are needed.

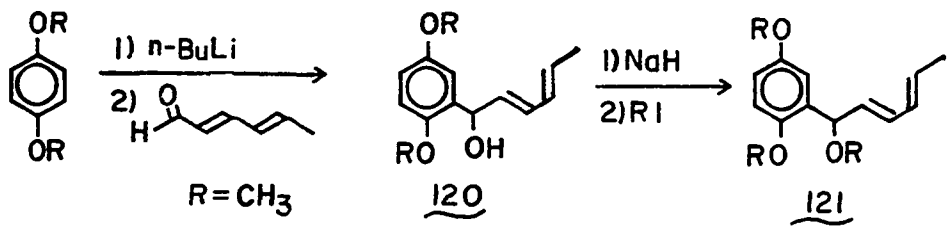
RESULTS AND DISCUSSION

Since their isolation, the anthracyclines have developed into an important class of antitumor agents. Their high biological activity, especially for the deoxyanthracyclines, has prompted considerable synthetic attention. Both the Diels-Alder reaction and the Friedel-Crafts reaction have played important roles in the synthesis of this class of compounds; however, relatively few syntheses have used a combination of these two powerful reactions. Since certain Lewis acids ($AlCl_3$, $BF_3 \cdot OEt_2$, $SnCl_4$, and $ZnCl_2$) are known to catalyze both the Diels-Alder and the Friedel-Crafts reaction, we anticipated that the tetracyclic skeleton of the anthracyclines could be rapidly constructed from the tandem Diels-Alder/Friedel-Crafts strategy shown below. Such a strategy is not only convergent and regiospecific, but it would also introduce the C-7 hydroxyl group via the carbon-carbon double bond.



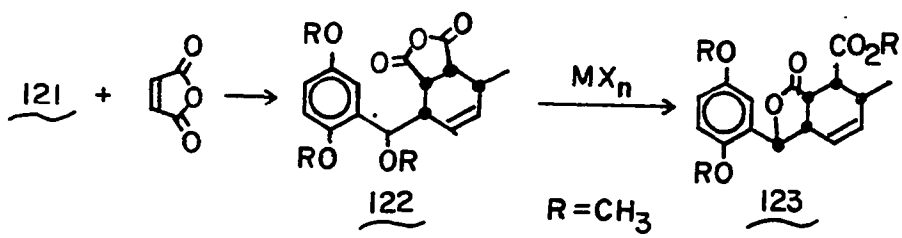
To test the viability of this strategy, diene 121 was chosen as a model system. Diene 121 was easily prepared by the lithiation of p-dimethoxybenzene and subsequent addition of 2,4-hexadienal to produce benzyl alcohol 120, which was unstable to chromatography. Methylation

of the crude alcohol afforded diene 121 in an excellent overall yield. Only decomposition of diene 121 was observed when the acid catalyzed reaction was attempted under a variety of conditions ($AlCl_3$, 0°C,



-78°C; $SnCl_4$, -78°C; $BF_3 \cdot OEt_2$, -78°C). As a result of this failure, we decided to examine a sequential Diels-Alder/Friedel-Crafts strategy.

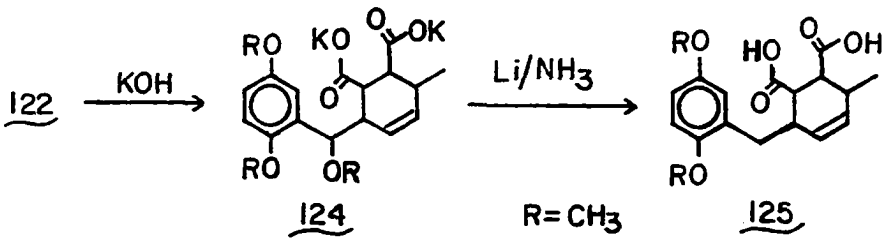
Cycloaddition of diene 121 with maleic anhydride gave adduct 122 in 77% yield. Adduct 122 was determined to be a single diastereomer by ^{13}C-NMR. While the cycloaddition is assumed to give the endo-product, the stereochemistry of the benzylic methoxyl group was not determined.



Treatment of adduct 122 with several Lewis acids ($AlCl_3$, $SnCl_4$, and $BF_3 \cdot OEt_3$) resulted in the formation of lactone 123 in 79% yield. Due to the good overall yield of lactone 123, we attempted to use this

unexpected product to our advantage. Numerous examples of hydrogenolysis of phthalides to the corresponding acids have been reported (88). However, all attempts to hydrogenolyze lactone 123 failed.

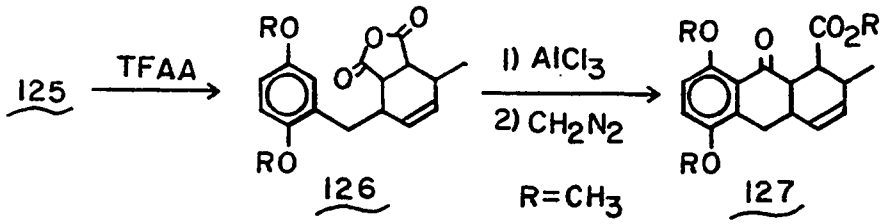
With the formation of lactone 123, it appeared necessary to remove the benzylic methoxyl group. Since dissolving metal reductions are known to deoxygenate benzyl alcohols (89), we anticipated the deoxygenation of adduct 122 via the biscarboxylate salt 124 (which



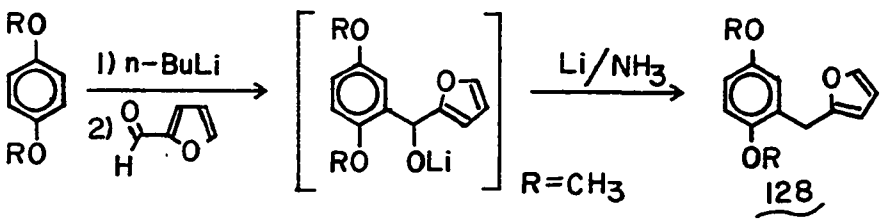
prevents the ammonolysis of the anhydride) would provide diacid 125. Hydrolysis of adduct 122 with potassium hydroxide and subsequent reduction with lithium/ammonia afforded diacid 125 in 89% yield. Diacid 125 was used without further purification.

While attempted cyclization with aluminum chloride resulted in the formation of an emulsion and the loss of the diacid, attempted cyclization with trifluoroacetic anhydride (TFAA) resulted in the formation of anhydride 126 in 70% yield. Cyclization was finally accomplished by treating anhydride 126 with aluminum chloride. Ketoester 127 was produced in 82% yield after esterification with diazomethane. The success of this cyclization demonstrated that the

Diels-Alder/Friedel-Crafts strategy can be a useful approach; however, the need to remove the benzylic methoxyl group makes this route very awkward. Unfortunately, all attempts to produce the deoxygenated diene failed.

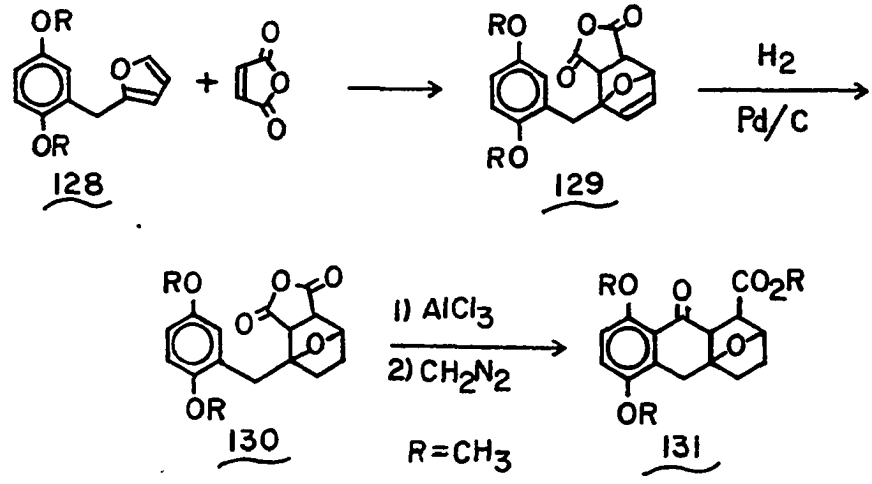


Because of the necessity of having a deoxygenated benzylic position and the success of the lithium/ammonia reduction, we believed that a furan ring would be an excellent choice for the diene moiety. Furans are known to readily undergo cycloaddition with maleic anhydride, are stable to the reduction conditions, and would allow us to easily incorporate the C-9 hydroxyl group. The required benzylfuran 128 was prepared by a tandem alkylation-reduction sequence (90) in 68% yield from p-dimethoxybenzene.



Since the failure of the tandem Diels-Alder/Friedel-Crafts strategy was due to the benzylic methoxyl group, we decided to reconsider this strategy with benzylfuran 128. As in the previous approach, all attempts to cyclize resulted in the decomposition of the benzylfuran. As a result, we focused our attention on the sequential Diels-Alder/-Friedel-Crafts strategy.

Cycloaddition of benzylfuran 128 with maleic anhydride was readily accomplished in the absence of light. In the presence of light, an unidentifiable mixture was formed. Boberg and Schultze have also reported a light sensitive cycloaddition of substituted furans with maleic anhydride (91). Adduct 129 was obtained in excellent yield by simple filtration. Since adduct 129 was found to undergo retro-cyclo-addition in solution, crude adduct was catalytically hydrogenated to provide anhydride 130 in 83% yield after recrystallization. Having synthesized anhydride 130 and having cyclized anhydride 126, we anticipated the cyclization of anhydride 130 would produce ketoester 131 under similar conditions.



However, this cyclization proved more difficult than anticipated. While reaction of anhydride 130 with aluminum chloride can demethylate starting material, reaction at ambient temperature provided the desired ketoester 131 in low yield. Because aluminum chloride can demethylate aryl methyl ethers, the low yield was probably due to this side reaction. Thus, other Lewis acids which do not demethylate aryl methyl ethers were tried. These results are summarized in Table 1.

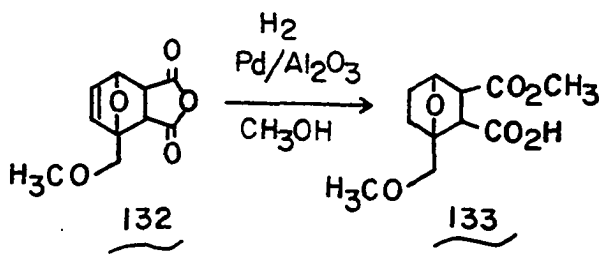
Table 1. Attempted cyclizations of anhydride 130

Lewis Acid	Solvent	Temperature	Result[a]
$AlCl_3$	CH_2Cl_2	0°C	S.M.
$AlCl_3$	CH_2Cl_2	25°C	131 (35%)
$AlCl_3$	CH_2Cl_2/CH_3NO_2	0°C	dec.
$AlCl_3$	CH_2Cl_2/CH_3NO_2	-20°C	S.M.
$SnCl_4$	CH_2Cl_2	25°C	S.M.
$SnCl_4$	$ClCH_2CH_2Cl$	85°C	S.M.
$TiCl_4$	CH_2Cl_2	25°C	S.M.
H_3PO_4	$ClCH_2CH_2Cl$	85°C	S.M.
$HClO_4$	CH_2Cl_2	25°C	S.M.

[a]S.M. = starting material; dec. = decomposition.

Due to the reluctance of anhydride 130 to cyclize, it appeared to us that the rigid [2.2.1] oxabicycloheptane system of anhydride 130 was preventing cyclization. Thus, we decided to modify this rigid ring system in the hope that cyclization could then be accomplished.

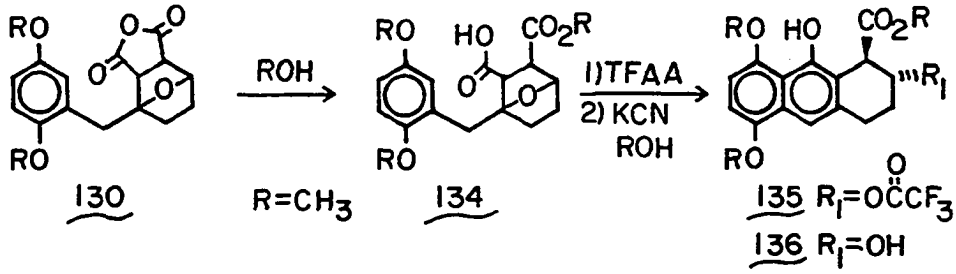
Yuldashev and Tsukervanik have reported the formation of acid 133 from methanolysis of anhydride 132 (92). The selectivity of the methanol addition is due to the attack at the least hindered carbonyl of the anhydride. This selectivity was also observed for similar systems.



132 133

Methanolysis of anhydride 130 provided acid 134 in quantitative yield. The regiochemistry of acid 134 was assumed to be as shown due to the attack at the least hindered carbonyl. This regiochemistry was proven to be correct by the cyclization of acid 134 to trifluoroacetate 135 with trifluoroacetic anhydride. The unexpected aromatization is attributed to the formation of trifluoroacetic acid (TFA) during the cyclization. The trifluoroacetic acid can enolize the ketone intermediate and can protonate the bridgehead oxygen. Cleavage of the bridgehead carbon-oxygen bond and acetylation of the hydroxyl group

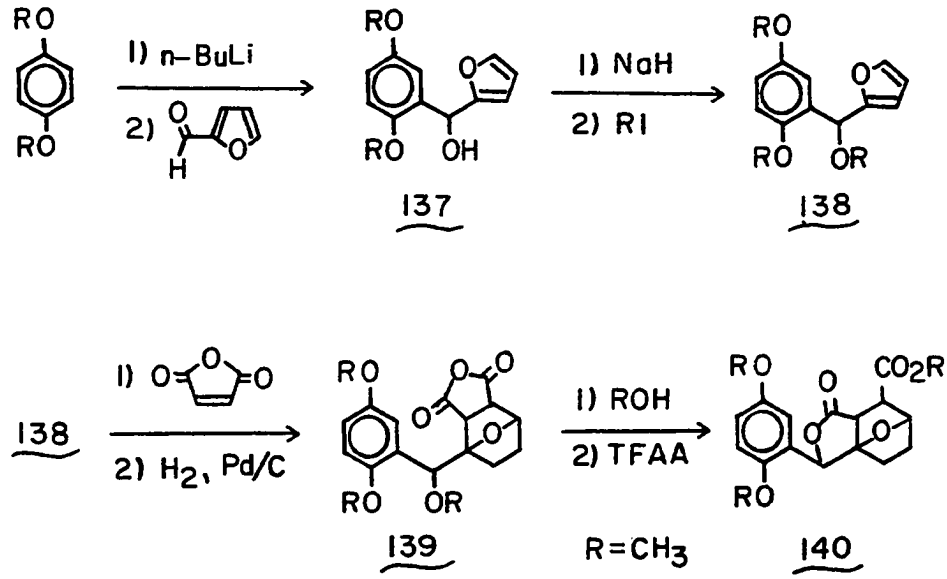
would produce trifluoroacetate 135. Because trifluoroacetate 135 was not stable to chromatography, the crude product was hydrolyzed to hydroxyester 136 with potassium cyanide in methanol (93). The overall



yield of hydroxyester 136 from acid 134 was 74%. Earlier attempts to hydrolyze the acetate with potassium carbonate in methanol (94) gave hydroxyester 136 in 50% yield. In the 300 MHz proton NMR of trifluoroacetate 135, the benzylic methine proton at 4.60 δ was a doublet with a coupling constant of 7 Hz, which is in good agreement with a trans-relationship between the trifluoroacetate and the carbomethoxy group. This stereochemistry indicates that the cycloaddition gave the endo-adduct, an assumption which is also supported by the chemical shifts of acid 134 (95).

After the successful cyclization of acid 134 without Lewis acids, we decided to determine if the benzylic methoxyl group could be present during cyclization. Thus, benzylfuran 138 was prepared in good overall yield by the methylation of benzyl alcohol 137 with sodium hydride and methyl iodide. Cycloaddition of benzylfuran 138 with maleic anhydride furnished the desired adduct; however, this product was extremely unstable and would decompose as a solid. Due to this instability,

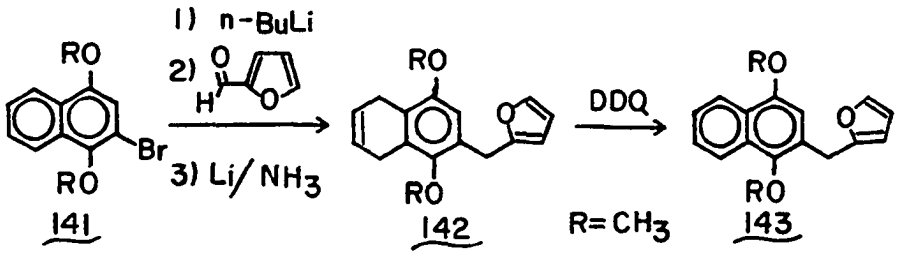
the crude adduct was immediately hydrogenated to afford anhydride 139, as a mixture of diastereomers, in 58% yield. Although adduct 122 was



produced as a single diastereomer, benzylfuran 138 gave a mixture of endo- and exo-adducts due to the retro-cycloaddition reaction (96). Methanolysis of anhydride 139 furnished the required acid in quantitative yield. However, attempted cyclizations of this acid with trifluoroacetic anhydride resulted in the formation of lactone 140. Thus, it is apparent that the benzylic methoxyl group cannot be present during cyclization.

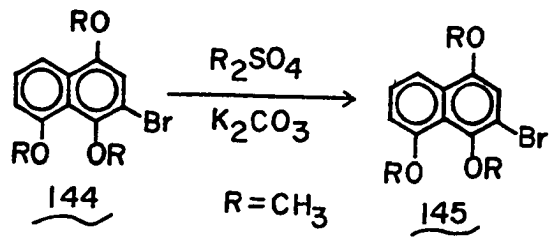
As a result of this failure, we directed our attention to the formation of a tetracyclic intermediate via the naphthylfuran 143. Initial attempts to prepare naphthylfuran 143 by the tandem alkylation-

reduction sequence resulted in the formation of dihydronaphthalene 142 from 2-bromo-1,4-dimethoxynaphthalene 141 (97). Dihydronaphthalene 142 could be converted into the desired naphthylfuran 143 with 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ); however, the overall yield was extremely poor. Due to the competitive reduction of the naphthalene

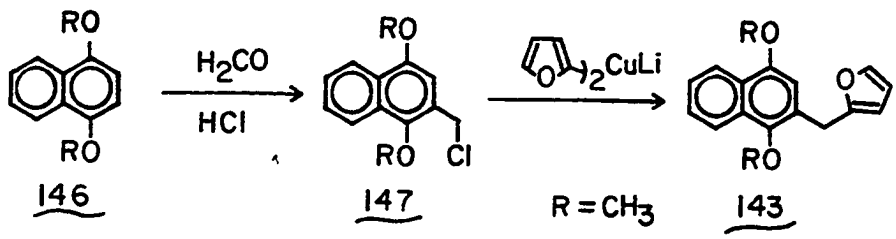


ring, other dissolving metal reductions ($Ca/NH_3/EtOH$ (98); $Zn/CuSO_4/NH_3$ (99)) and ionic hydrogenations (Et_3SiH/TFA (100); $NaBH_4/TFA$ (101)) were tried, but all failed to give the desired product. Ionic hydrogenation with triethylsilane and boron trifluoride etherate (102) produced naphthylfuran 143, but in only 20% yield.

We anticipated that the introduction of an electron-donating methoxyl group to the unsubstituted naphthalene ring would prevent the competitive reduction of this ring. The required naphthalene, 3-bromo-1,4,5-trimethoxynaphthalene 145, was prepared in excellent yield by the methylation of 2-bromo-4,8-dimethoxynaphthol 144 (103). Unfortunately, the tandem alkylation-reduction with the trimethoxynaphthalene 145 resulted in the formation of a complex mixture.

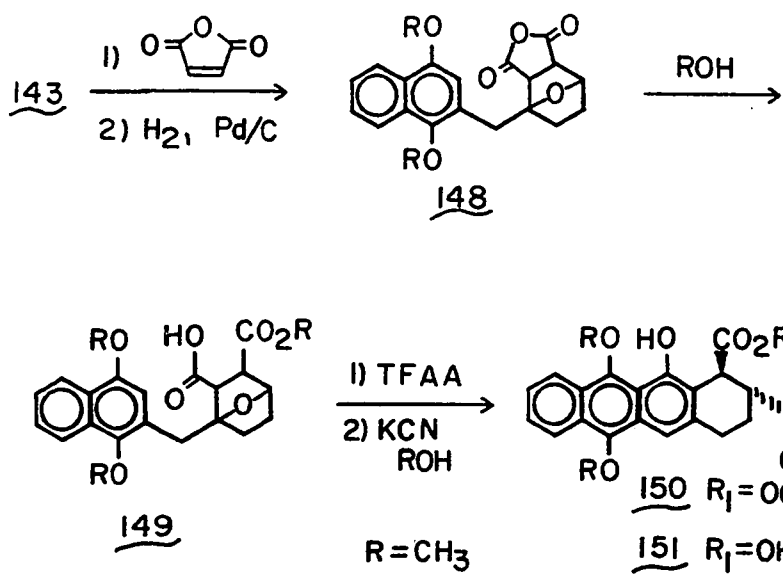


Naphthylfuran 143 was finally obtained in good overall yield via a cuprate coupling. Chloromethylation (104) of 1,4-dimethoxynaphthalene 146 (97) produced 2-chloromethyl-1,4-dimethoxynaphthalene 147. Coupling naphthalene 147 with di(2-furyl)copper lithium afforded napthylfuran 143 in an overall yield of 50% from inexpensive and readily available starting materials.



Cycloaddition of napthylfuran 143 with maleic anhydride at ambient temperature and subsequent catalytic hydrogenation provided anhydride 148 in an overall yield of 64%. As in the previous cases, methanolysis of anhydride 148 furnished acid 149 in quantitative yield. Treatment of acid 149 with trifluoroacetic anhydride afforded the chromatographically unstable trifluoroacetate 150, which was hydrolyzed with

potassium cyanide to the hydroxyester 151. The overall yield for this cyclization-hydrolysis sequence was 74%. The trans-stereochemistry of the hydroxyl and carbomethoxyl groups is supported again by proton NMR.



Having successfully constructed the tetracyclic skeleton of the anthracyclines, we directed our attention to the functionalization of hydroxyester 151. We had envisioned the introduction of the C-9 ethyl sidechain by a Grignard reaction on the corresponding ketoester. Smith and Leuenberg have investigated the oxidation of β-hydroxyesters (105) and have reported that the Swern oxidation gave good to excellent yields of the ketoesters. Furthermore, oxidation with pyridinium chlorochromate, 2,3-dichloro-5,6-dicyanobenzoquinone, Jones' reagent,

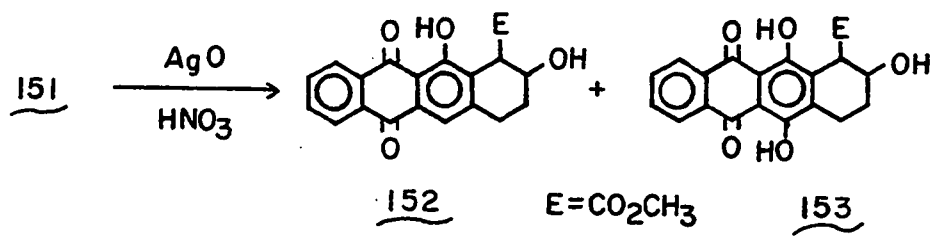
and manganese dioxide gave poor results due to the β-elimination of water and the competitive oxidation of the resulting enol. Swern oxidation of hydroxyester 151 resulted in the formation of an unidentifiable purple oil. Because this failure may have resulted from the oxidation of the phenolic B ring, we decided to protect the phenolic hydroxyl as the methyl ether.

Attempted methylation with dimethylsulfate and potassium carbonate failed to give the desired product. Since the C-11 phenolic hydroxyl is highly chelated, attempts to methylate it with silver (I) oxide and methyl iodide (106) were tried; however, only starting material was obtained. An attempt to methylate the phenolic hydroxyl with diazomethane (107) also failed. Because the C-11 phenolic hydroxyl was reluctant to methylate, we had to reexamine the possibility of oxidizing hydroxyester 151 without protection.

Jung and Brown have reported the selective oxidation of secondary alcohols in the presence of primary alcohols with trityl tetrafluoroborate (108). Due to the bulkiness of this reagent, we anticipated that it would not interact with the C-11 hydroxyl group. This proved to be the case; however, only starting material was isolated from the reaction. A final attempt to oxidize hydroxyester 151 with N,N'-dicyclohexylcarbodiimide and ortho-phosphoric acid in dimethylsulfoxide was tried. Although this oxidation gave good results for the oxidation of β-hydroxyesters in indole alkaloids (109), only starting material

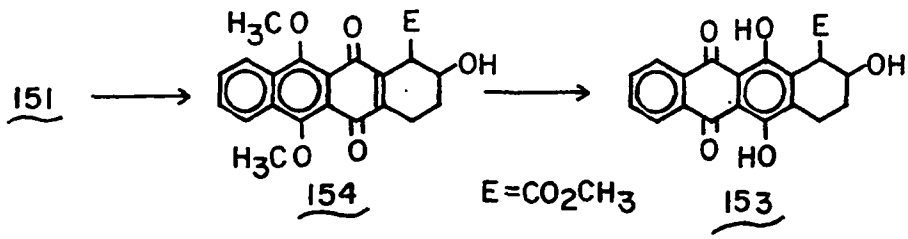
was obtained with hydroxyester 151. With the failure to oxidize hydroxyester 151, the C-9 ethyl sidechain must be introduced at the furan stage of the synthesis.

Since hydroxyester 151 was formed rapidly and efficiently, we decided to transform hydroxyester 151 into a 9-dealkyl anthracyclinone. Oxidative demethylation (110) of hydroxyester 151 gave an inseparable mixture of anthraquinones 152 and 153. Formation of this mixture is supported by the three phenolic hydroxyl peaks in the proton NMR and by the molecular ion peaks (368 and 352 m/e) in the mass spectrum. Attempts to convert hydroxyester 151 directly into anthraquinone 153 by varying the temperature of the reaction and the equivalents of silver (II) oxide (111) failed. Since attempts to convert this mixture to anthraquinone 153 by resubmitting it to the oxidation condition also failed, formation of anthraquinone 153 presumably results from the oxidation of the B ring prior to the C ring. Because Boeckman and coworkers have recently reported the transformation of a 6-deoxy-anthraquinone to the 6-hydroxyanthraquinone (112), the mixture of anthraquinones 152 and 153 could be converted to anthraquinone 153.

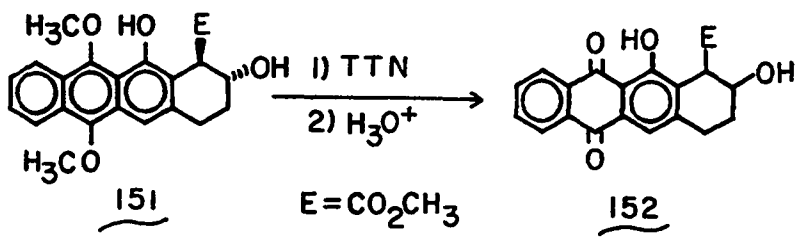


152 E=CO_2CH_3 153

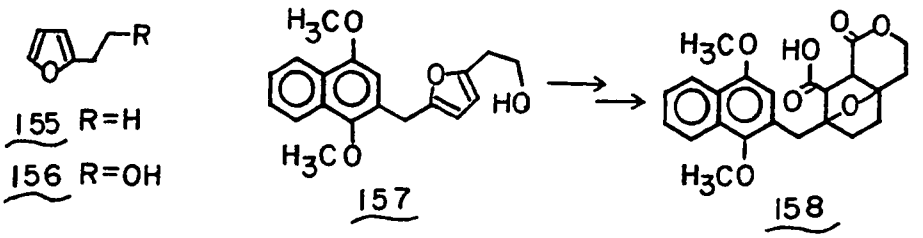
However, we believed a more rapid and efficient approach to anthraquinone 153 could be accomplished by the oxidation of hydroxyester 151 to anthraquinone 154. Oxidative demethylation and reductive work-up would provide anthraquinone 153. A similar approach has been used by Hauser and Prasanna (113). Due to the highly chelated nature of the C-11 hydroxyl group, attempts to oxidize hydroxyester 151 to anthraquinone 154 with Fremy's salt (114) failed. Since thallium trinitrate (TTN) oxidizes phenols to the corresponding quinones by attacking the para-position (115), we anticipated the formation of



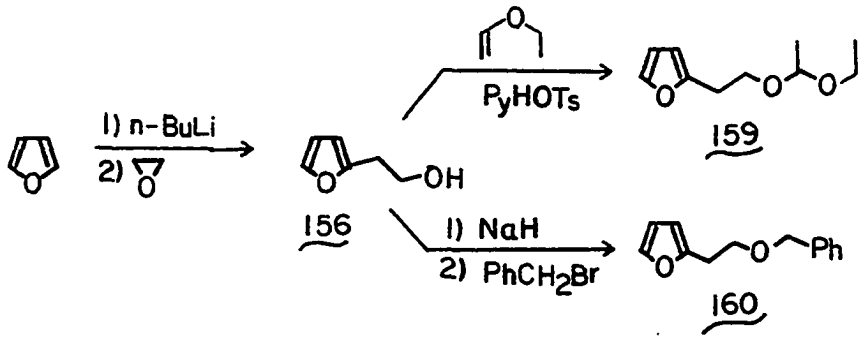
anthraquinone 154 with thallium trinitrate. However, oxidation of hydroxyester 151 resulted in the unexpected formation of anthraquinone 152 in 70% yield after recrystallization. With the formation of anthraquinone 152, which could be converted to anthraquinone 153, we directed our attention to the incorporation of the C-9 ethyl sidechain into our synthesis.



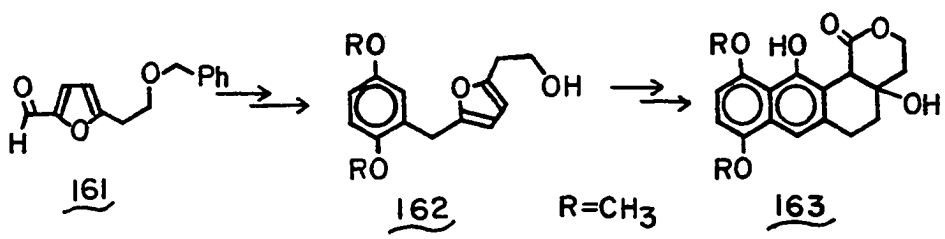
Although 2-ethylfuran 155 is commercially available and would introduce the C-9 ethyl sidechain, we anticipated a decrease in the selectivity of the methanol addition. However, conversion of furan 156 to naphthylfuran 157 would allow for the selective formation of acid 158 via an intramolecular attack of the hydroxyl group. Furan 156 was



prepared in 71% yield by the addition of ethylene oxide to 2-furyl lithium. Protection of the primary alcohol with ethyl vinyl ether produced furan 159 in excellent yield. Although similar furans have been metallated with two or three equivalents of n-butyllithium (116), all attempts to metallate furan 159 with one equivalent of n-butyllithium failed. Since we could not use a large excess of alkyl lithium due to the cuprate formation, furan 156 was converted to furan 160 in the hope that metallation could be accomplished. However, furan 160 could not be metallated. Attempts to prepare the dianion of furan 156 also failed. With the failure to metallate furans 159 and 160, the naphthylfuran 157 could not be formed via the cuprate coupling strategy.

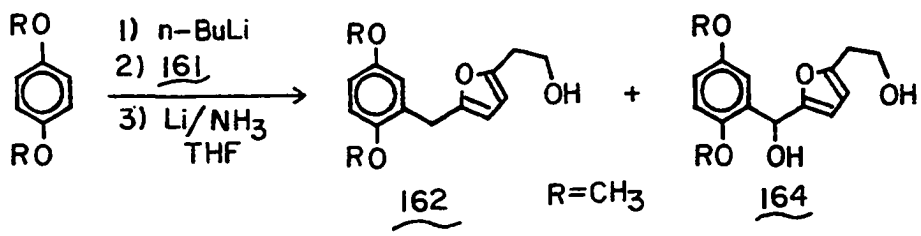


Since furans can be formylated in excellent yields (117), we envisioned the formation of benzylfuran 162 from aldehyde 161 via the tandem alkylation-reduction sequence. Conversion of benzylfuran 162 to lactone 163 and subsequent cycloaddition would produce the linear tetracyclic skeleton of the anthracyclines.

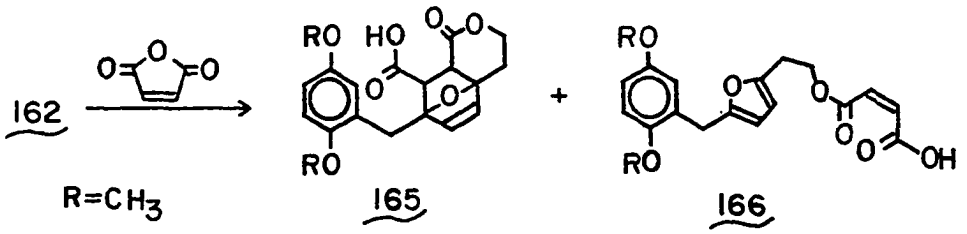


Vilsmeier-Haack formylation ($POCl_3$/DMF) of furan 160 afforded aldehyde 161 in 86% yield. Tandem alkylation-reduction of aldehyde 161 with lithiated p-dimethoxybenzene produced a mixture of benzylfurans 162 and 164. Although benzylfuran 162 was formed only in trace

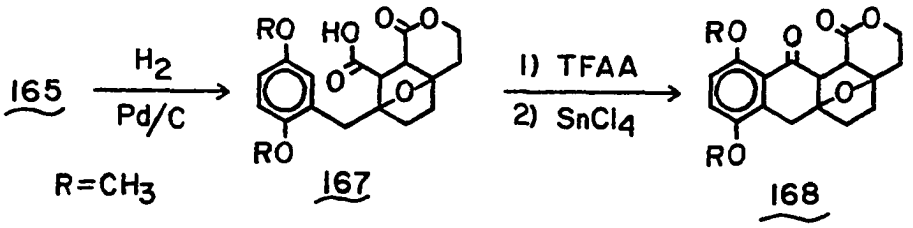
amounts, resubmitting the crude mixture to the same reduction conditions afforded benzylfuran 162 in an overall yield of 63%. The failure to produce benzylfuran directly was attributed to the generation of the insoluble bisalkoxide salt of benzylfuran 164. This salt could be observed precipitating from the solution. Attempts to form benzylfuran 162 directly by increasing the ratio of tetrahydrofuran and by adding a proton source (ethanol, t-butanol, and acetic acid) failed. Although benzylfuran 162 could not be formed directly, it could be produced in gram quantities by sequential reductions.



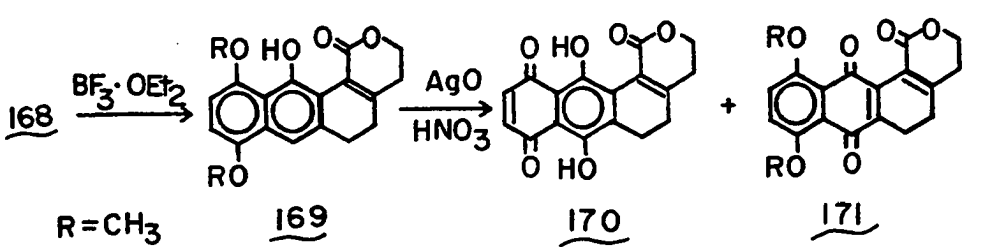
Cycloaddition of benzylfuran 162 with maleic anhydride at ambient temperature and simple filtration of the reaction mixture afforded adduct 165 in 75% yield. Concentration of the filtrate resulted in a mixture of starting materials and ester 166. Attempts to convert this mixture to adduct 165 failed. Imagawa and coworkers have also reported the formation of a similar mixture and the failure of the intramolecular cyclization (118).



Hydrogenation of adduct 165 gave acid 167 in 80% yield after recrystallization. Due to the insolubility of acid 167, it was characterized as the methyl ester. While treatment of acid 167 with trifluoroacetic anhydride for short reaction times (6 hrs) afforded starting material, longer reaction times (18 hrs) resulted in the decomposition of the starting material. However, acid 167 could be cyclized by treating the mixed anhydride (formed from TFAA) with tin tetrachloride (119). Using this reaction sequence, ketolactone 168 was isolated in 85% yield.

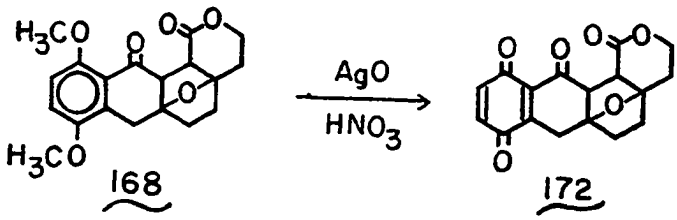


Since the cyclization of acid 167 produced ketolactone 168 instead of the desired lactone 163, we investigated the transformation of the ketolactone into lactone 163. As in the case of the hydroxy-esters 136 and 151, we anticipated the aromatization of ketolactone 168 with trifluoroacetic acid. However, treatment of ketolactone 168 with trifluoroacetic acid resulted in either the isolation or de-composition of the starting material. This result explains why cyclization with trifluoroacetic anhydride could not be accomplished. Since Lewis acids can enolize carbonyls, we decided to attempt the aromatization with Lewis acids. Treatment of ketolactone 168 with boron trifluoride etherate afforded lactone 169 in 67% yield. Although the aromatization also resulted in the elimination of the β-hydroxyl group, introduction of the β-hydroxyl via epoxidation and reduction has been reported (45).



Oxidative demethylation of lactone 169 produced a mixture of quinones 170 and 171. This mixture proved difficult to separate and could only be partially resolved. Attempts to form quinone 170 selectively by varying the reaction temperature and the equivalents of

silver (II) oxide failed. Due to the formation of quinones 170 and 171, we decided to prepare ketoquinone 172 from ketolactone 168. Oxidative demethylation of ketolactone 168 afforded ketoquinone 172; however, it proved difficult to purify and was used without purification. Cycloaddition of ketoquinone 172 with 1-acetoxy-1,3-butadiene in refluxing benzene resulted in the formation of a complex mixture. The formation of these mixtures is due to the instability of ketoquinone 172, instability which has been observed in similar systems (120). While this work was in progress, John Walling had successfully deoxygenated diaryl carbinols with sodium borohydride and boron trifluoride etherate in diglyme (121). Anticipating the formation of

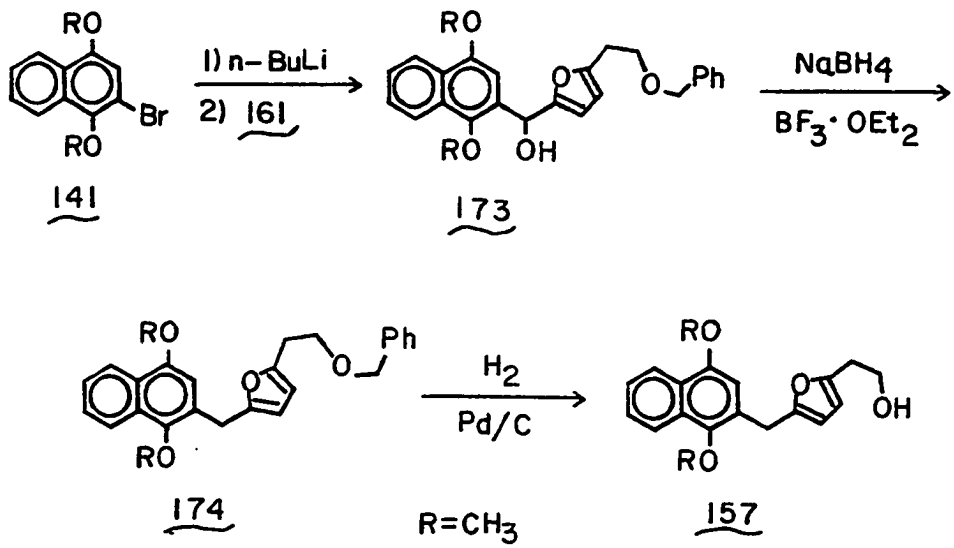


168 172

naphthylfuran 157 from this reaction, we focused our attention on the synthesis of naphthylfuran 157.

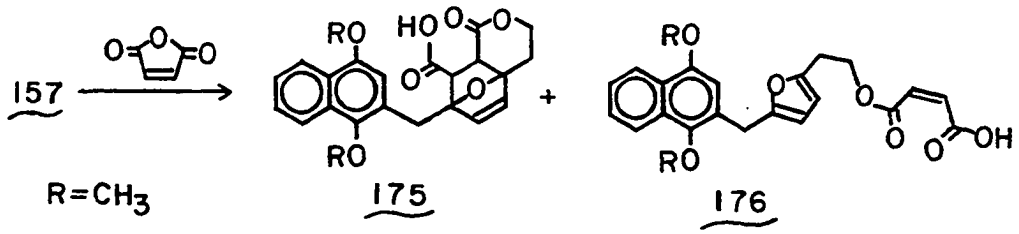
Metallation of 2-bromo-1,4-dimethoxynaphthalene 141 in diethyl ether at -78°C and addition of aldehyde 161 afforded furyl alcohol 173. Due to the extreme instability of furyl alcohol 173, the concentrated alcohol was immediately diluted with dry tetrahydrofuran and was reduced with sodium borohydride and boron trifluoride etherate

to produce naphthylfuran 174. The formation of naphthylfuran 174 was very erratic, with yields ranging from 48% to 61%.

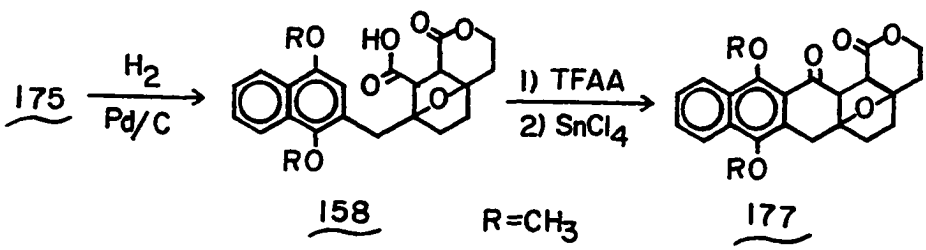


141 173 174 157

Since naphthylfuran 174 failed to react with maleic anhydride, the benzyl ether was hydrolyzed to produce naphthylfuran 157 in 93% yield. Cycloaddition of naphthylfuran 157 with maleic anhydride afforded adduct 175 in 60% yield. As in the cycloaddition of benzylfuran 162, concentration of the filtrate resulted in a mixture of starting materials and ester 176. While this mixture could not be converted to adduct 175, it could be converted to naphthylfuran 157 by refluxing with lithium hydroxide in methanol. Thus, the overall yield of adduct 175 based on recovered naphthylfuran was 81%.



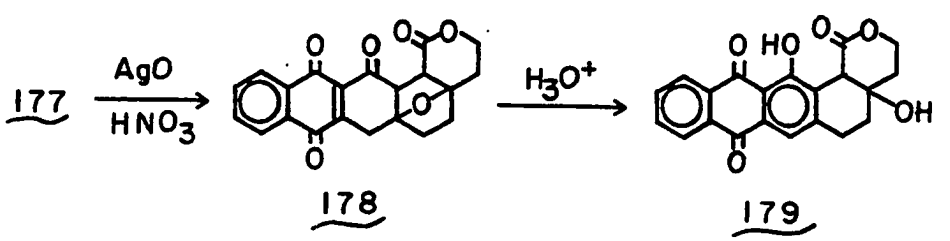
Hydrogenation of crude adduct 175 afforded acid 158 in 95% yield. Both proton and carbon NMR indicated a mixture of diastereomers; however, the ratio of this mixture was greater than 10:1. Because attempts to recrystallize acid 158 produced an oil, the crude solid was used without purification. Cyclization of acid 158 with trifluoroacetic anhydride/tin tetrachloride gave ketolactone 177. Recrystallization of the crude ketolactone 177 afforded a single diastereomer in 75% yield. This diastereomer was highly crystalline (monoclinical) and has been submitted for a single crystal X-ray determination.



While aromatization of ketolactone 168 was accomplished with boron trifluoride etherate, treatment of ketolactone 177 with this Lewis acid resulted in the formation of a complex mixture which could not be

separated. In the hope that aromatization could be accomplished with a trifluoroacetic acid/trifluoroacetic anhydride mixture, we attempted this aromatization; however, only decomposition products were isolated.

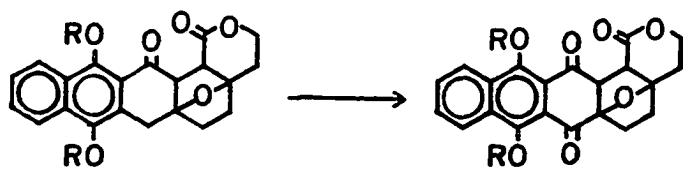
As a result of these initial failures, we anticipated a more facile aromatization could occur by the enolization of ketoquinone 178. Oxidative demethylation of ketolactone 177 produced ketoquinone 178, which when dissolved in deuterated chloroform afforded a red precipitate. This precipitate was shown to be the anthraquinone 179. Treatment of the crude ketoquinone 178 with a catalytic amount of concentrated hydrochloric acid precipitated anthraquinone 179 in extremely poor yield (20%). Concentration of the filtrate afforded an unidentifiable material. Attempts to aromatize ketoquinone 178 with acetic acid also produced anthraquinone 179, but in lower yields.



178 179

The sequential Diels-Alder/Friedel-Crafts strategy has afforded a rapid route to the anthracycline skeleton. However, this strategy is plagued by the poor conversion of ketolactone 177 to anthraquinone 179. The reason for this poor conversion is not obvious. Due to this poor conversion, other strategies for aromatization must be tried. One such strategy is the benzylic oxidation of ketolactone 177 with

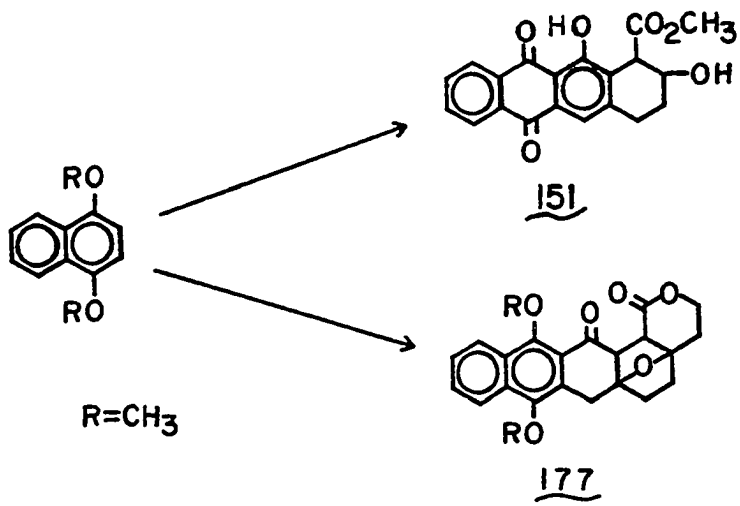
2,3-dichloro-5,6-dicyanobenzoquinone (122), which would produce diketone 180. Cleavage of the carbon-oxygen bond should occur easily with zinc in acetic acid (123). This strategy would also introduce the C-6 hydroxyl group. Since boron trifluoride etherate is only capable of monodentate coordination, the use of a bidentate Lewis acid ($TiCl_4$ or $SnCl_4$) may provide more selectivity in the aromatization and represents a second possibility. Aromatization of ketolactone 177 under basic conditions may also be possible.



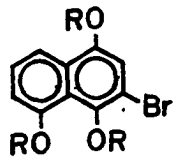
177 $R=CH_3$ 180

CONCLUSION

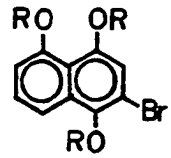
The sequential Diels-Alder/Friedel-Crafts strategy has proven to be an effective approach for the expedient formation of anthracycline intermediates. While anthraquinone 151 can be formed in only 8 steps in an overall yield of 16%, ketolactone 177 can be formed in 7 steps in an overall yield of 25%. These syntheses are extremely short, proceed in good yield, use inexpensive starting materials, and produce highly functionalized intermediates. Moreover, anthraquinone 151 and ketolactone 177 are generated from a common starting material. This



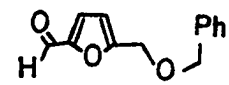
approach is also very versatile. Use of napthalenes 145 and 181 or aldehyde 182 would allow for the rapid formation of several novel anthracycline analogues.



145



181



182

R=CH_3

EXPERIMENTAL

General

Unless otherwise noted, materials were obtained from commercial suppliers and were used without purification. Tetrahydrofuran and diethyl ether were distilled from lithium aluminium hydride prior to usage. Dichloromethane was distilled from phosphorus pentoxide. All reactions were conducted under a nitrogen atmosphere, and all extracts were dried over anhydrous sodium sulfate. Melting points were determined on a Fisher-Johns melting point apparatus and are uncorrected. Infrared spectra were obtained on a Beckman IR-4250 or Acculab 2 spectrometer. Nuclear magnetic resonance spectra were determined on a Varian EM-360 spectrometer. High field (300 MHz) proton spectra were obtained using a Nicolet Magnetics Corporation NMC-1280 spectrometer. All chemical shifts are reported in δ relative to tetramethylsilane as an internal standard. Carbon-13 NMR spectra were determined on a JOEL FX-90Q or Nicolet NMC-1280 spectrometer and are reported in ppm relative to the central peak of $CDCl_3$ (77.06 ppm). High resolution mass spectra were recorded on a AEI-MS 902 high resolution mass spectrometer. Low resolution mass spectra were recorded on a Finnegan 4023 mass spectrometer. Elemental analyses were determined by Galbraith Laboratories, Inc.

1-(2,5-Dimethoxyphenyl)-1-methoxyhexa-2,4-diene 121

To a solution of 1,4-dimethoxybenzene (3.00 g, 21.7 mmol) in 15 ml of ether at 0°C was added n-butyllithium (22 mmol). The solution was allowed to warm to room temperature and was stirred for 24 hrs. The

solution was cooled to -78°C and distilled 2,4-hexadienal (2.39 ml, 21.7 mmol) in 10 ml of ether was added. The reaction was warmed to room temperature and was quenched with water. The aqueous phase was extracted three times with ether. The extracts were combined, washed with water and brine, dried, and concentrated to afford crude 120 as a yellow oil. NMR ($CDCl_3$) δ 1.82 (d, 3 H, J = 6 Hz), 3.70 (s, 6 H), 5.21 - 6.30 (m, 5 H), 6.68 - 6.82 (m, 3 H). IR (film) 3440, 3010, 2950, 2820, 1600, 1495, 1460, 1270, 1220, 1175, 1040, 985 cm^{-1}.

To a suspension of sodium hydride (30 mmol) in 15 ml of THF at 0°C was added crude 120 in 20 ml of THF. The mixture was stirred for 20 minutes. Methyl iodide (30 mmol) was added, and the mixture was stirred at room temperature for 7 hrs. The reaction was poured into ice water and the aqueous phase was extracted three times with ether. The extracts were combined, washed with water and brine, dried, and concentrated. The residue was chromatographed on silica gel using 6:1 hexane/ether to yield 4.10 g (76%) of 121 as a colorless oil. NMR ($CDCl_3$) δ 1.82 (d, 3 H, J = 6 Hz), 3.30 (s, 3 H), 3.74 (s, 6 H), 5.05 (d, 1 H, J = 6 Hz), 5.40 - 6.30 (m, 4 H), 6.68 - 6.83 (m, 2 H), 6.88 - 7.00 (m, 1 H). C-13 NMR 18.01, 55.73, 56.25, 56.38, 77.32, 112.05, 112.50, 113.28, 129.54, 130.39, 130.91, 131.10, 131.30, 151.07, 154.06 ppm. IR (film) 3010, 2980, 2840, 1500, 1460, 1275, 1215, 1080, 1045, 990 cm^{-1}.

4-[(2,5-Dimethoxyphenyl)methoxymethyl]-7-methyl-4,7,8,9-tetrahydroisobenzofuran-1,3-dione 122

To a solution of 121 (1.45 g, 5.85 mmol) in 5 ml of ether was added maleic anhydride (0.57 g, 5.85 mmol). The flask was sealed with a septum and the reaction was stirred for 24 hrs. The solid was filtered, washed with 4:1 hexane/ether, and dried in vacuo. Recrystallization from acetone/hexane yielded 1.53 g (77%) of 122 (mp 153 - 155°C). NMR ($CDCl_3$) δ 1.35 (d, 3 H, J = 7 Hz), 2.23 - 2.78 (m, 4 H), 3.22 (s, 3 H), 3.76 (s, 3 H), 3.82 (s, 3 H), 5.30 (d, 1 H, J = 11 Hz), 6.63 (br s, 2 H), 6.78 - 6.90 (m, 3 H). C-13 NMR 16.32, 30.76, 43.18, 43.64, 45.91, 55.73, 56.19, 56.38, 74.46, 112.11, 113.35, 113.80, 129.61, 129.80, 134.61, 152.37, 154.25, 171.49, 171.81 ppm. IR ($CDCl_3$) 3010, 2940, 2840, 1850, 1775, 1500, 1460, 1275, 1260, 1045, 950, 925 cm^{-1}. Elemental analysis calculated for $C_{19}H_{22}O_6$: C, 65.88; H, 6.40. Found: C, 65.65; H, 6.64.

7-Carbomethoxy-3-(2,5-dimethoxyphenyl)-6-methyl-3a,6,7,7a-tetrahydro-3H-isobenzofuran-1-one 123

To a solution of 122 (0.346 g, 1 mmol) in 5 ml of dichloromethane at 0°C was added tin tetrachloride (0.35 ml, 3 mmol). The solution was stirred for 1 hr at 0°C. The reaction was poured into ice water and was extracted three times with dichloromethane. The extracts were combined, washed with water, dried, and concentrated. Recrystallization from acetone/hexane yielded 0.266 g (79%) of 123 (mp 128 - 130°C). NMR ($CDCl_3$) δ 1.20 (d, 3 H, J = 7 Hz), 2.95 - 3.30 (m, 4 H), 3.70 (s, 3 H),

3.78 (s, 3 H), 3.85 (s, 3 H), 5.00 - 5.80 (m, 3 H), 6.72 (br s, 3 H). C-13 NMR 18.08, 33.62, 35.51, 42.33, 44.61, 52.22, 55.67, 55.80, 75.63, 110.88, 113.02, 113.61, 123.69, 126.74, 134.48, 149.24, 153.34, 169.34, 172.85 ppm. IR ($CDCl_3$) 3005, 2960, 2850, 1770, 1740, 1500, 1465, 1360, 1275, 1220, 1050 cm^{-1}. Elemental analysis calculated for $C_{19}H_{22}O_6$: C, 65.88; H, 6.40. Found: C, 66.06; H, 6.34.

4,5-Dicarboxy-3-[(2,5-dimethoxyphenyl)methyl]-6-methylcyclohex-1-ene 125

To a solution of 122 (0.547 g, 1.60 mmol) in 2 ml of THF was added 4 ml of 1N KOH. The reaction was stirred for 3 hrs at room temperature. The reaction mixture was diluted with 20 ml of benzene and was concentrated in vacuo. This process was repeated three times. The crude solid was suspended in 10 ml of THF. Approximately 20 ml of liquid ammonia was then added. Small pieces of lithium wire (3.5 mmol) were added, and the reaction was stirred for 15 minutes. The reaction was quenched with solid ammonium chloride, and the ammonia was allowed to evaporate. The residue was partitioned between brine and ether, was acidified with 6N HCl, and extracted with ether two times. The extracts were combined, dried, and concentrated to yield 0.483 g (89%) of 125 (mp 173 - 176°C). NMR ($CDCl_3$) δ 1.12 (d, 3 H, J = 7 Hz), 2.50 - 3.20 (m, 6 H), 3.75 (s, 6 H), 5.55 (br s, 2 H), 6.70 (s, 3 H), 9.40 (br s, 2 H). IR ($CDCl_3$) 3400 - 2450 (br) 1720, 1500, 1465, 1430, 1280, 1225, 1045 cm^{-1}.

4-[(2,5-Dimethoxyphenyl)methoxymethyl]-7-methyl-3a,4,7,7a-tetrahydro-isobenzofuran-1,3-dione 126

To a solution of 125 (1.39 g, 4.16 mmol) in 10 ml of dichloromethane was added 0.75 ml of trifluoroacetic anhydride (5.2 mmol) at 0°C. After stirring for 6 hrs at room temperature, the reaction was concentrated in vacuo. Recrystallization from acetone/hexane yielded 0.918 g (70%) of 126 (mp 167 - 168°C). NMR ($CDCl_3$) δ 1.35 (d, 3 H, J = 7 Hz), 3.05 - 3.40 (m, 6 H), 3.76 (s, 6 H), 5.65 - 5.90 (m, 2 H), 6.73 (s, 2 H), 6.90 (br s, 1 H). C-13 NMR 16.26, 30.56, 31.54, 35.96, 44.87, 46.24, 55.67, 55.80, 111.40, 111.98, 117.51, 128.89, 133.77, 134.09, 151.98, 153.47, 171.29, 172.01 ppm. IR ($CDCl_3$) 2940, 2840, 1850, 1775, 1500, 1465, 1225, 1040 cm^{-1}. Elemental analysis calculated for $C_{18}H_{20}O_5$: C, 68.34; H, 6.37. Found: C, 67.91; H, 6.16.

1-Carbomethoxy-5,8-dimethoxy-2-methyl-9-oxo-1,2,4a,9,9a,10-hexahydro-anthracene 127

To a solution of 126 (0.130 g, 0.41 mmol) in 3 ml of dichloromethane at 0°C was added aluminum chloride (0.134 g, 1.0 mmol) in small portions. After stirring for 8 hrs at 0°C, the reaction mixture was poured into ice water. The aqueous phase was extracted three times with dichloromethane. The extracts were combined, washed with water, dried, and concentrated. The crude solid was dissolved in dichloromethane and esterified with diazomethane. The reaction mixture was concentrated and chromatographed on silica gel using 1:1 hexane/ether (10% CH_2Cl_2) as the solvent. Chromatography yielded 0.112 g (82%) of 127 (mp 117 -

119°C). NMR ($CDCl_3$) δ 1.13 (d, 3 H, J = 7 Hz), 2.90 (br s, 3 H), 3.18 (m, 3 H), 3.48 (s, 3 H), 3.65 (s, 3 H), 3.73 (s, 3 H), 5.48 (br s, 2 H), 6.65 (d, 1 H, J = 8 Hz), 6.88 (d, 1 H, J = 8 Hz). C-13 NMR 18.47, 26.40, 31.54, 33.30, 45.00, 48.25, 50.98, 56.32, 110.10, 116.08, 123.56, 128.56, 132.53, 133.57, 149.96, 153.67, 173.24, 197.43 ppm. IR ($CDCl_3$) 3015, 2960, 2850, 1745, 1660, 1495, 1460, 1265, 1200, 1090, 1030 cm^{-1}. MS (m/e) 330, 315, 298, 283, 271, 255, 230, 217, 178, 151.

2-[(2,5-Dimethoxyphenyl)methyl]furan 128

To a solution of 1,4-dimethoxybenzene (2.00 g, 14.6 mmol) in 10 ml of ether at 0°C was added n-butyllithium (14.9 mmol). After warming to room temperature, the solution was stirred for 24 hrs. The solution was then cooled to -78°C and distilled furfural (1.20 ml, 14.5 mol) in 10 ml of THF was added. The yellow solution was stirred at -78°C for 15 minutes. Approximately 30 ml of liquid ammonia was then added followed by small pieces of lithium wire (32 mmol). The reaction was stirred for 30 minutes. Solid ammonium chloride was added, and the ammonia was allowed to evaporate. The residue was partitioned between ether and brine. The organic phase was dried and concentrated. The yellow oil was chromatographed on silica gel using 2:1 hexane/dichloromethane as solvent. Chromatography afforded 2.15 g (68%) of 128 as a colorless oil. NMR ($CDCl_3$) δ 3.74 (s, 6 H), 3.91 (s, 2 H), 5.91 (d, 1 H, J = 3 Hz), 6.14 - 6.28 (m, 1 H), 6.58 - 6.80 (m, 3 H), 7.20 (d, 1 H, J = 2 Hz). C-13 NMR 22.35, 55.45, 56.05, 106.06, 110.16, 111.62, 114.58, 116.34, 127.91, 141.05, 151.45, 153.47, 154.12 ppm. IR (film)

3010, 2950, 2840, 1595, 1500, 1460, 1280, 1220, 1040, 800, 730 cm^{-1}. High resolution mass spectrum for $C_{13}H_{14}O_3$ requires 218.0943; measured 218.0938.

4-[(2,5-Dimethoxyphenyl)methyl]-3a,4,7,7a-tetrahydro-4,7-epoxyisobenzofuran-1,3-dione 129

To a solution of 128 (5.00 g, 22.9 mmol) in 20 ml of ether was added maleic anhydride (2.25 g, 22.9 mmol). The flask was sealed with a septum and was covered with tin foil. The solution was stirred for 24 hrs, diluted with 10 ml of hexane, and filtered. The solid was washed with 4:1 hexane/ether and dried in vacuo to yield 6.16 g (85%) of 129. NMR ($CDCl_3$) δ 3.09 - 3.35 (m, 4 H), 3.72 (s, 3 H), 3.78 (s, 3 H), 5.27 (br s, 1 H), 6.28 (br s, 2 H), 6.63 - 7.02 (m, 3 H). IR ($CDCl_3$) 1855, 1785, 1500, 1465, 1280, 1230, 1090, 1050 cm^{-1}.

4-[(2,5-Dimethoxyphenyl)methyl]hexahydro-4,7-epoxyisobenzofuran-1,3-dione 130

To a suspension of activated 10% Pd/C (0.60 g) in acetone (15 ml) under a hydrogen atmosphere was added the crude 129 (6.16 g, 19.5 mmol) in 40 ml of acetone. The suspension was stirred for 6 hrs, filtered through celite, and concentrated in vacuo. The residue was filtered through a small column of silica gel using 1:1 hexane/dichloromethane solution and was recrystallized from hexane/dichloromethane to yield 5.14 g (83%) of 130 (mp 160 - 162°C). NMR ($CDCl_3$) δ 1.20 - 1.90 (m, 4 H), 3.19 (s, 3 H), 3.33 (s, 1 H), 3.72 (s, 3 H), 3.74 (s, 3 H), 4.77 - 4.92 (m, 1 H), 6.71 (br s, 2 H), 6.90 - 7.02 (m, 1 H). C-13 NMR 29.46,

29.65, 30.89, 52.15, 52.87, 55.67, 55.99, 79.47, 89.74, 111.59, 112.83, 117.77, 125.57, 151.91, 153.47, 170.05, 171.55 ppm. IR ($CDCl_3$) 1875, 1790, 1505, 1470, 1235, 1095, 1050 cm^{-1}. Elemental analysis calculated for $C_{17}H_{18}O_6$: C, 64.14; H, 5.70. Found: C, 63.91; H, 5.75.

1-Carbomethoxy-5,8-dimethoxy-9-oxo-1,3,4,9,9a,10-hexahydro-2H-2,4a-epoxyanthracene 131

To a solution of 130 (0.102 g, 0.32 mmol) in 3 ml of dichloromethane at 0°C was added aluminum chloride (0.094 g, 0.704 mmol). The red suspension was stirred at 0°C for 2 hrs and at room temperature for 3 hrs. The suspension was cooled to 0°C. Nitromethane (0.5 ml) which prevents the formation of an emulsion was added followed by 6N HCl (4 ml). The reaction was diluted with water and extracted with dichloromethane. The extracts were combined, washed with water, dried, and concentrated. The crude residue was dissolved in dichloromethane and esterified with diazomethane. Concentration and chromatography on silica gel using 2:1 ether/hexane (10% CH_2Cl_2) yielded 0.036 g (35%) of 131 (mp 178 - 181°C). NMR δ 1.58 - 1.90 (m, 4 H), 2.83 - 3.42 (m, 4 H), 3.57 (s, 3 H), 3.76 (s, 3 H), 3.79 (s, 3 H), 4.58 (d, 1 H, J = 4 Hz), 6.75 (d, 1 H, J = 9 Hz), 6.96 (d, 1 H, J = 9 Hz). C-13 NMR 26.08, 30.76, 34.66, 51.96, 55.99, 56.45, 57.36, 79.14, 83.39, 111.01, 115.75, 123.43, 129.80, 150.15, 153.47, 171.62, 196.52 ppm. IR ($CDCl_3$) 1960, 1730, 1675, 1590, 1480, 1435, 1265, 1070 cm^{-1}. MS (m/e) 332, 314, 301, 288, 273, 255, 229, 216, 201, 177, 163, 115, 91, 77, 55.

2-Carboxy-3-carbomethoxy-1-[(2,5-dimethoxyphenyl)methyl]-7-oxabicyclo-[2.2.1]heptane 134

A solution of 130 (1.00 g, 3.14 mmol) in 10 ml of dry methanol (dried with molecular sieves) was refluxed for 6 hrs. The solution was cooled to room temperature and was concentrated in vacuo. The residue was dissolved in a sodium bicarbonate solution. The bicarbonate solution was washed with ether, acidified with 6N HCl, and extracted with dichloromethane. The extracts were combined, washed with water, dried, and concentrated to yield 1.08 g (98%) of 134 (mp 141 - 143°C). NMR ($CDCl_3$) δ 1.32 - 1.72 (m, 4 H), 2.89 - 3.40 (m, 4 H), 3.64 (s, 3 H), 3.72 (s, 6 H), 5.05 (br s, 1 H), 6.68 - 6.82 (m, 2 H), 6.96 (br s, 1 H), 9.87 (br s, 1 H). C-13 NMR 30.04, 30.43, 31.54, 51.96, 53.32, 55.73, 55.86, 56.58, 88.64, 111.40, 113.09, 117.31, 126.03, 151.78, 153.34, 171.29, 176.23 ppm. IR ($CDCl_3$) 3360 - 2930 (br), 1740, 1710, 1500, 1465, 1435, 1225, 1050 cm^{-1}. Elemental analysis calculated for $C_{18}H_{22}O_7$: C, 61.71; H, 6.33. Found: C, 61.63; H, 6.30.

trans-1-Carbomethoxy-2,9-dihydroxy-5,8-dimethoxy-1,2,3,4-tetrahydro-anthracene 136

To a solution of 134 (0.350 g, 1 mmol) in 10 ml of dichloromethane at 0°C was added trifluoroacetic anhydride (0.29 ml, 2.05 mmol). The reaction was warmed to room temperature and was stirred 6 hrs. The reaction was then diluted with 30 ml carbon tetrachloride and concentrated in vacuo to afford crude 135. NMR ($CDCl_3$) δ 1.94 - 2.45 (m, 2 H), 2.97 - 3.28 (m, 2 H), 3.77 (s, 3 H), 3.95 (s, 3 H), 4.02 (s, 3 H),

4.60 (d, 1 H, J = 7 Hz), 5.28 - 5.70 (m, 1 H), 6.60 (s, 2 H), 7.58 (s, 1 H), 9.87 (s, 1 H). IR ($CDCl_3$) 3460, 2980, 2860, 1790, 1740, 1640, 1615, 1520, 1460, 1440, 1375, 1310, 1255, 1225, 1170, 1065 cm^{-1}.

To a solution of crude 135 in 10 ml of dry methanol was added several crystals of potassium cyanide. After stirring for 6 hrs at room temperature, the solution was neutralized with 1N HCl and concentrated in vacuo. The residue was dissolved in dichloromethane. The dichloromethane was washed with water, dried, and concentrated. The crude solid was filtered through a small column of silica gel using 2:1 dichloromethane/ethyl acetate solution and was then recrystallized from dichloromethane/hexane to yield 0.246 g (74%) of 136 (mp 204 - 206°C). NMR ($CDCl_3$) δ 1.83 - 2.20 (m, 2 H), 2.90 - 3.28 (m, 2 H), 3.72 (s, 3 H), 3.90 (s, 3 H), 3.98 (s, 3 H), 4.18 - 4.40 (m, 2 H), 6.54 (s, 2 H), 7.50 (s, 1 H), 9.78 (s, 1 H). C-13 NMR 27.83, 28.03, 46.30, 52.15, 55.73, 56.19, 68.48, 102.29, 102.81, 111.85, 127.26, 135.98, 149.83, 152.11, 173.89 ppm. IR ($CDCl_3$) 3540, 3300, 3060, 2955, 1735, 1620, 1500, 1430, 1370, 1265, 1065 cm^{-1}. Elemental analysis calculated for $C_{18}H_{20}O_6$: C, 65.08; H, 6.07. Found: C, 64.28; H, 6.01.

Hydrolysis of trifluoroacetate 135 via potassium carbonate was accomplished by adding the crude 135 (1 mmol) to a degassed methanol/tetrahydrofuran (1:1) solution at 0°C. Potassium carbonate (2 mmol) was added. After stirring for 2 hrs at 0°C, the solution was neutralized and concentrated. The residue was dissolved in dichloromethane. The dichloromethane was washed with water, dried, and concentrated. Chromatography afford 0.167 g (50%) of 136.

2-[(2,5-Dimethoxyphenyl)methoxymethyl]furan 138

Alcohol 137 was prepared from p-dimethoxybenzene (4.00 g, 29 mmol) and distilled furfural (2.40 ml, 29 mmol) using the procedure developed for 120. NMR ($CDCl_3$) δ 3.72 (s, 6 H), 5.88 - 6.27 (m, 3 H), 6.75 (s, 2 H), 6.82 - 6.93 (m, 1 H), 7.21 - 7.35 (m, 1 H). IR (film) 3450, 2960, 2840, 1500, 1465, 1377, 1240, 1180, 1150, 1040, 820, 740 cm^{-1}.

Methylation of crude 137 using the procedure developed for 121 afforded 138. Crude 138 was filtered through silica gel using 1:1 ether/-hexane and was then recrystallized from ether/hexane to yield 4.94 g (69%) of 138 (mp 62 - 63°C). NMR ($CDCl_3$) δ 3.36 (s, 3 H), 3.70 (s, 3 H), 3.78 (s, 3 H), 5.60 (s, 1 H), 5.98 (d, 1 H, J = 4 Hz), 6.13 - 6.28 (m, 1 H), 6.74 (d, 2 H, J = 3 Hz), 7.04 - 7.17 (m, 1 H), 7.27 - 7.35 (m, 1 H). C-13 NMR 55.73, 56.32, 56.97, 72.31, 108.01, 110.03, 112.05, 113.15, 113.93, 128.56, 142.35, 151.20, 153.99, 154.32 ppm. IR ($CDCl_3$) 3040, 2950, 2850, 1500, 1465, 1280, 1240, 1080, 1050 cm^{-1}.

4-[(2,5-Dimethoxyphenyl)methoxymethyl]hexahydro-4,7-epoxyisobenzo-furan-1,3-dione 139

Cycloaddition of 138 (1.50 g, 6.05 mmol) with maleic anhydride (0.59 g, 6.04 mmol) was accomplished using the procedure developed for 129. The crude solid was immediately hydrogenated using the procedure developed for 130. The crude 139 was chromatographed on silica gel using 1:1 ether/hexane (10% CH_2Cl_2) as solvent to yield 1.22 g (58%) of 139 as a mixture of diastereomers (mp 122 - 147°C). NMR ($CDCl_3$) δ 1.52 - 1.98 (m, 4 H), 3.31 - 3.35 (br s, 5 H), 3.80 and 3.85 (two s,

6 H), 4.78 - 4.93 (m, 1 H), 5.12 and 5.27 (two s, 1 H), 6.73 - 6.84 (m, 2 H), 7.07 - 7.28 (m, 1 H). IR ($CDCl_3$) 2940, 2820, 1855, 1770, 1487, 1455, 1257, 1210, 1080, 1035 cm^{-1}. Elemental analysis calculated for $C_{18}H_{20}O_7$: C, 62.06; H, 5.79. Found: C, 61.60; H, 5.80.

7-Carbomethoxy-3-(2,5-dimethoxyphenyl)-6-methylhexahydro-3H-3a,6-epoxyisobenzofuran-1-one 140

Using the methanolysis conditions of 134, anhydride 139 was converted to the carbomethoxyacid in quantitative yield (mp 70 - 89°C). NMR ($CDCl_3$) δ 1.40 - 2.06 (m, 4 H), 3.25 - 3.49 (m, 4 H), 3.64 - 3.79 (m, 10 H), 4.57 - 4.76 (m, 1 H), 5.06 and 5.23 (two s, 1 H), 6.74 - 6.89 (m, 2 H), 7.04 - 7.20 (m, 1 H), 8.88 (br s, 1 H). IR ($CDCl_3$) 3400 - 2820 (br), 1740, 1705, 1490, 1455, 1425, 1270, 1240, 1210, 1165, 1080, 1035 cm^{-1}. Elemental analysis calculated for $C_{19}H_{24}O_8$: C, 59.99; H, 6.36. Found: C, 59.14; H, 6.38.

Attempted cyclization of the carbomethoxyacid (0.217 g, 0.57 mmol) via the procedure developed for 136 resulted in the formation of lactone 140. The crude product was chromatographed on silica gel using 1:1:1 dichloromethane/ether/hexane as solvent. Chromatography afforded 0.149 g (75%) of 140 as a viscous oil. NMR ($CDCl_3$) δ 1.43 - 2.00 (m, 4 H), 3.02 (s, 1 H), 3.26 - 3.85 (m, 10 H), 5.00 - 5.19 (m, 2 H), 6.71 - 6.85 (m, 2 H), 6.90 - 7.04 (m, 1 H). IR ($CDCl_3$) 3005, 2970, 2930, 1785, 1740, 1500, 1470, 1435, 1250, 1220, 1155, 1040 cm^{-1}. MS (m/e) 348, 330, 302, 271, 257, 225, 181, 165, 151, 113.

2-[(5,8-Dihydro-1,4-dimethoxy-2-naphthalenyl)methyl]furan 142

To a solution of 2-bromo-1,4-dimethoxynaphthylene (97) (1.10 g, 4.14 mmol) in 5 ml of THF at -78°C was added n-butyllithium (4.20 mmol). After stirring for 10 minutes, furfural (0.34 ml, 4.14 mmol) was added in 10 ml of THF. The reaction mixture was stirred for an additional 30 minutes. Approximately 50 ml of liquid ammonia was added followed by lithium wire (16.6 mmol). The reaction mixture was stirred for 30 minutes, solid ammonium chloride was added, and the ammonia was allowed to evaporate. The residue was partitioned between ether and brine. The organic phase was dried, filtered, and concentrated in vacuo. Chromatography using 2:1 hexane/dichloromethane provided 0.61 g (54%) of 142 as a colorless oil. NMR ($CDCl_3$) δ 3.28 (br s, 4 H), 3.67 (s, 3 H), 3.72 (s, 3 H), 4.00 (s, 2 H), 5.84 - 6.05 (m, 3 H), 6.20 - 6.34 (m, 1 H), 6.55 (s, 1 H), 7.22 (br s, 1 H). IR (film) 3040, 2945, 2850, 1600, 1480, 1460, 1428, 1340, 1230, 1105, 1080, 1010 cm^{-1}.

2-[(1,4-Dimethoxy-2-naphthalenyl)methyl]furan 143

a. Method A To a solution of 142 (0.50 g, 1.85 mmol) in 15 ml of benzene was added 3,4-dichloro-5,6-dicyano-1,4-benzoquinone (0.42 g, 1.86 mmol). The dark red solution was refluxed for 20 hrs and was then filtered. The filtrate was diluted with ether, washed with 1N NaOH, water, and brine, dried, and concentrated. Chromatography using 2:1 hexane/dichloromethane afforded 0.247 g (50%) of 143 as a colorless oil.

b. Method B To a solution of furan (5.70 ml, 78.5 mmol) in 50 ml of ether at 0°C was added n-butyllithium (78.5 mmol). The solution was stirred for 1 hr at room temperature. The precipitated 2-furyl lithium was dissolved with 15 ml of THF. The solution was then transferred by a cannula to a suspension of cuprous iodide (7.50 g, 39.5 mmol) in 50 ml THF at 0°C. After the addition of dimethyl sulfide (6.0 ml, 81 mmol), the dark solution was stirred for 30 minutes at 0°C. A solution of 2-chloromethyl-1,4-dimethoxynaphthalene (2.87 g, 12.2 mmol) in 20 ml of THF was added and the reaction was allowed to warm slowly to room temperature. The reaction was protected from light with tin foil and was stirred for 18 hrs. The reaction mixture was poured into ammonium chloride and extracted with ether. The extracts were combined, washed with brine, dried, filtered, and concentrated. The crude product was chromatographed on silica gel using 4:1 hexane/-dichloromethane to afford 3.56 g (80%) of 143 as a colorless oil. NMR ($CDCl_3$) δ 3.89 (s, 6 H), 4.15 (s, 2 H), 6.00 (d, 1 H, J = 3 Hz), 6.20 - 6.34 (m, 1 H), 6.64 (s, 1 H), 7.30 - 7.58 (m, 3 H), 7.92 - 8.33 (m, 2 H). C-13 NMR 28.61, 55.54, 62.23, 105.54, 106.26, 110.29, 121.87, 122.32, 125.12, 125.77, 126.55, 128.63, 141.38, 147.10, 151.85, 154.51 ppm. IR ($CDCl_3$) 3005, 2975, 2850, 1600, 1520, 1465, 1370, 1270, 1165, 1120, 1090, 1005 cm^{-1}. High resolution mass spectrum for $C_{17}H_{16}O_3$ requires 268.10995; measured 268.11091.

3-Bromo-1,4,5-trimethoxynaphthalene 145

To a solution of 2-bromo-4,8-dimethoxynaphthol (103) (2.20 g, 7.77 mmol) in 40 ml of acetone was added dimethyl sulfate (0.94 ml, 10.0 mmol) and potassium carbonate (1.93 g, 14.0 mmol). The reaction mixture was refluxed for 24 hrs, filtered, and concentrated in vacuo. The crude product was chromatographed on silica gel using 3:1 hexane/-dichloromethane as solvent to yield 2.10 g (91%) of 145 (mp 82 - 84°C). NMR ($CDCl_3$) δ 3.81 (s, 3 H), 3.88 (s, 3 H), 3.95 (s, 3 H), 6.73 - 6.94 (m, 2 H), 7.28 (t, 1 H, J = 8 Hz), 7.83 (d, 1 H, J = 8 Hz). IR ($CDCl_3$) 3010, 2980, 2950, 2850, 1588, 1515, 1465, 1417, 1345, 1270, 1080 cm^{-1}. MS (m/e) 298, 296, 283, 281, 202, 187, 174, 159, 129.

2-Chloromethyl-1,4-dimethoxynaphthalene 147

Gaseous HCl was passed through a solution of 37% aqueous formaldehyde (3.0 ml) and concentrated HCl (1.4 ml) in 6.0 ml of dioxane for 15 minutes. The rate of HCl gas was controlled so that the internal temperature of the solution was maintained between 55 - 60°C. A solution of 1,4-dimethoxynaphthalene (97) (4.00 g, 21.2 mmol) in 12 ml of dioxane was added over a 20 minute period. After the addition was complete, the gaseous HCl addition was stopped. The reaction was cooled to room temperature and was poured into ice water. The aqueous phase was extracted with ether. The extracts were combined, washed with water and brine, dried, filtered, and concentrated in vacuo. Chromatography on silica gel using 9:1 hexane/dichloromethane afforded 3.22 g (64%) of 147 (mp 64 - 65°C). NMR ($CDCl_3$) δ 3.96 (s, 6 H),

4.83 (s, 2 H), 6.75 (s, 1 H), 7.40 - 7.59 (m, 2 H), 7.96 - 8.32 (m, 2 H). C-13 NMR 41.42, 55.53, 62.88, 104.37, 122.13, 122.39, 125.25, 126.03, 126.81, 128.30, 147.75, 152.10 ppm. IR ($CDCl_3$) 3080, 2940, 2850, 1630, 1600, 1515, 1460, 1370, 1270, 1225, 1160, 1125, 1095, 1030, 1000 cm^{-1}.

4-[(1,4-Dimethoxy-2-naphthalenyl)methyl]hexahydro-4,7-epoxyisobenzofuran-1,3-dione 148

Cycloaddition of 143 (3.00 g, 11.2 mmol) with maleic anhydride (1.10 g, 11.2 mmol) in 9 ml of ether was accomplished using the procedure developed for 129. The precipitate was filtered and washed with 4:1 hexane/ether to yield 2.99 g of crude product. NMR ($CDCl_3$) δ 3.32 (s, 3 H), 3.44 (s, 1 H), 3.94 (s, 6 H), 5.31 (br s, 1 H), 6.30 (br s, 2 H), 6.89 (s, 1 H), 7.30 - 7.67 (m, 2 H), 7.95 - 9.33 (m, 2 H). IR ($CDCl_3$) 3080, 3005, 2940, 2840, 1850, 1780, 1625, 1593, 1458, 1365, 1260, 1225, 1085, 995 cm^{-1}.

The crude product was hydrogenated using the procedure developed for 130. Chromatography and recrystallization afforded 2.64 g (overall yield of 64%) of 148 (mp 163 - 164°C). NMR ($CDCl_3$) δ 1.30 - 1.75 (m, 4 H), 3.27 (s, 2 H), 3.52 (d, 2 H, J = 5 Hz), 3.88 (s, 3 H), 3.97 (s, 3 H), 4.97 (br s, 1 H), 6.98 (s, 1 H), 7.34 - 7.60 (m, 2 H), 7.88 - 8.27 (m, 2 H). C-13 NMR 29.52, 30.37, 31.08, 52.02, 53.13, 55.73, 62.10, 79.73, 89.87, 106.65, 121.93, 122.39, 124.21, 125.31, 126.03, 126.55, 128.30, 147.81, 151.65, 170.23, 171.49 ppm. IR ($CDCl_3$)

3060, 2950, 2840, 1870, 1785, 1625, 1595, 1458, 1370, 1260, 1225, 1085, 995, 935 cm^{-1}. Elemental analysis calculated for $C_{21}H_{20}O_6$: C, 68.47; H, 5.47. Found C, 68.47; H, 5.52.

2-Carboxy-3-carbomethoxy-1-[(1,4-dimethoxy-2-naphthalenyl)methyl]-7-oxabicyclo[2.2.1]heptane 149

Using the methanolysis conditions of 134, anhydride 148 was converted to 149 in quantitative yield (mp 161 - 164°C). NMR ($CDCl_3$) δ 1.22 - 1.76 (m, 4 H), 3.00 - 3.43 (m, 4 H), 3.68 (s, 3 H), 3.79 (s, 3 H), 3.93 (s, 3 H), 5.06 (br s, 1 H), 6.95 (s, 1 H), 7.38 - 7.60 (m, 2 H), 7.72 - 8.25 (m, 2 H). C-13 NMR 29.78, 30.30, 31.41, 51.44, 52.48, 55.54, 56.77, 61.58, 76.47, 87.99, 106.32, 106.65, 121.48, 121.87, 124.53, 125.25, 125.96, 127.72, 147.03, 150.87, 171.49, 173.89 ppm. IR ($CDCl_3$) 3450 - 2430 (br), 1745, 1710, 1600, 1463, 1375, 1268, 1230, 1090 cm^{-1}. Elemental analysis calculated for $C_{22}H_{24}O_7$: C, 65.99; H, 6.04. Found: C, 65.74; H, 6.18.

trans-1-Carboxy-2,12-dihydroxy-6,11-dimethoxy-1,2,3,4-tetrahydronaphthacene 151

Using the cyclization conditions of 136, acid 149 (0.817 g, 2.04 mmol) was converted to 150 with trifluoroacetic anhydride (0.59 ml, 4.18 mmol) in 20 ml dichloromethane. MHz 300, NMR ($CDCl_3$) δ 2.09 - 2.21 (m, 1 H), 2.45 - 2.61 (m, 1 H), 3.08 - 3.29 (m, 1 H), 3.28 - 3.40 (m, 1 H), 3.76 (m, 3 H), 4.06 (s, 3 H), 4.07 (s, 3 H), 4.72 (d, 1 H, J = 7 Hz), 5.51 - 5.58 (m, 1 H), 7.42 - 7.53 (m, 2 H), 7.61 (s,

1 H), 8.09 - 8.18 (m, 1 H), 8.22 - 8.30 (m, 1 H), 10.21 (s, 1 H). IR ($CDCl_3$) 3555, 2960, 1785, 1735, 1640, 1450, 1365, 1220, 1160, 1045 cm^{-1}.

Potassium cyanide/methanol hydrolysis of 150 afforded 151. Chromatography on silica gel using 4:2:1 ether/hexane/dichloromethane yielded 0.576 g (74%) of 151 (mp 154 - 155°C). MHz 300, NMR ($CDCl_3$) δ 2.02 - 2.10 (m, 1 H), 2.16 - 2.27 (m, 1 H), 2.73 (br s, 1 H), 2.99 - 3.11 (m, 1 H), 3.28 - 3.37 (m, 1 H), 3.78 (s, 3 H), 4.07 (s, 3 H), 4.09 (s, 3 H), 4.32 - 4.45 (m, 2 H), 7.43 - 7.50 (m, 2 H), 7.61 (s, 1 H), 8.11 - 8.18 (m, 1 H), 8.21 - 8.27 (m, 1 H), 10.12 (s, 1 H). C-13 NMR 27.96, 28.22, 46.50, 52.09, 62.88, 64.31, 68.48, 111.59, 114.26, 114.78, 121.67, 122.71, 123.17, 125.12, 125.31, 125.57, 135.46, 147.42, 148.33, 151.33, 152.30, 173.76 ppm. IR ($CDCl_3$) 3680 - 3260 (br), 2950, 1730, 1650, 1435, 1360, 1350, 1190, 1165, 1045 cm^{-1}. Elemental analysis calculated for $C_{22}H_{22}O_6$: C, 69.10; H, 5.80. Found: C, 66.89; H, 6.06. High resolution mass spectrum for $C_{22}H_{22}O_6$ requires 382.14164; measured 382.14307.

trans-Carbomethoxy-2,12-dihydroxy-1,2,3,4-tetrahydronaphthacene-6,11-dione 152

a. Attempted preparation with silver (II) oxide/nitric acid To a solution of 151 (0.050 g, 0.13 mmol) in 2 ml of THF at room temperature was added silver (II) oxide (III) (0.064 g, 0.52 mmol). After the addition of 0.13 ml of 6N HNO_3, the reaction mixture was stirred for 5 minutes. The reaction mixture was poured into water and extracted with dichloromethane. The extracts were combined, washed with water

and brine, dried, and concentrated *in vacuo*. Chromatography on silica gel using 2:2:1 hexane/ethyl acetate/dichloromethane provided a mixture of 152 and 153 (0.034 g). NMR ($CDCl_3$) δ 1.78 - 2.17 (m), 2.70 - 3.15 (m), 3.76 (s), 4.12 - 4.40 (m), 7.50 - 8.42 (m), 13.10 (s), 13.33 (s), 13.46 (s). IR ($CDCl_3$) 3600 - 3380 (br), 1725, 1690, 1585, 1350, 1270 cm^{-1}. MS (m/e) 368 (M+), 352 (M+), 308, 291, 275, 264.

b. Preparation with thallium trinitrate To a solution of thallium (III) nitrate trihydrate (0.930 g, 2.09 mmol) in 3 ml of methanol at 0°C was added 151 (0.382 g, 1.00 mmol) in 7 ml of methanol. The reaction mixture was stirred for 1 hr at 0°C and was then filtered. The filtrate was concentrated *in vacuo*, and the residue was dissolved in 10 ml of THF. After the addition of 2 ml 1N HCl, the reaction was stirred for 10 hrs. The reaction was diluted with dichloromethane. The organic phase was washed with water, dried, and concentrated *in vacuo*. Recrystallization from hot methanol provided 0.246 g (70%) of 152 (mp 259 - 262°C). MHz 300, NMR ($CDCl_3$) δ 2.01 - 2.19 (m, 2 H), 2.73 (br s, 1 H), 2.88 - 3.03 (m, 1 H), 3.14 - 3.27 (m, 1 H), 3.78 (s, 3 H), 4.25 - 4.37 (m, 2 H), 7.64 (s, 1 H), 7.77 - 7.83 (m, 2 H), 8.27 - 8.33 (m, 2 H), 13.14 (s, 1 H). C-13 NMR 27.07, 28.34, 45.86, 52.22, 67.06, 113.30, 119.91, 126.72, 127.24, 128.69, 131.27, 133.20, 133.55, 134.03, 134.42, 146.86, 161.20, 172.13, 182.31, 188.00 ppm. IR ($CDCl_3$) 3540 - 3300 (br), 2940, 1725, 1650, 1345, 1050 cm^{-1}. UV (MeOH) 227, 246, 261, 327, 405 nm. Elemental analysis calculated for $C_{20}H_{16}O_6$: C, 68.18; H, 4.58. Found: C, 65.84; H, 5.08. High

resolution mass spectrum for $C_{20}H_{16}O_6$ requires 352.09469; measured 352.09605.

2-(2-Furyl)ethanol 156

To a solution of furan (10.0 ml, 137 mmol) in 100 ml of ether at 0°C was added n-butyllithium (150 mmol). The reaction was stirred for 3 hrs at room temperature and was then cooled to 0°C. Ethylene oxide (10.0 ml, 200 mmol) was slowly added, and the reaction was stirred for 1 hr. The reaction mixture was poured into water and was then extracted with ether. The extracts were combined, washed with brine, dried, and concentrated in vacuo. Distillation afforded 10.86 g (71%) of 156 (bp 40°C, 3 mm Hg). NMR ($CDCl_3$) δ 2.42 (br s, 1 H), 2.87 (t, 2 H, J = 7 Hz), 3.85 (t, 2 H, J = 7 Hz), 6.10 (d, 1 H, J = 4 Hz), 6.23 - 6.38 (m, 1 H), 7.29 - 7.40 (m, 1 H). C-13 NMR 31.41, 60.74, 106.19, 110.09, 141.24, 152.82 ppm. IR (film) 3560 - 3100 (br), 2900, 1585, 1490, 1130, 1030, 710 cm^{-1}.

Ethyl vinyl ether of 2-(2-furyl)ethanol 159

To a solution of 156 (14.54 g, 138 mmol) and ethyl vinyl ether (18.0 ml, 188 mmol) in 200 ml of dichloromethane was added pyridinium tosylate (2.00 g, 7.97 mmol) at room temperature. The reaction mixture was stirred for 10 hrs and was then concentrated. Chromatography on silica gel using 8:1 hexane/ether as solvent afforded 22.8 g (90%) of 159 as a colorless liquid. NMR ($CDCl_3$) δ 1.05 - 1.32 (m, 6 H), 2.88 (t, 2 H, J = 7 Hz), 3.30 - 3.87 (m, 4 H), 4.68 (q, 1 H, J = 6 Hz), 6.04

(d, 1 H, J = 4 Hz), 6.18 - 6.25 (m, 1 H), 7.22 - 7.32 (m, 1 H). C-13 NMR 15.28, 19.77, 29.07, 60.80, 63.01, 99.56, 105.93, 110.23, 141.05, 153.21 ppm. IR (film) 2990, 2920, 1605, 1510, 1450, 1385, 1345, 1140, 1090, 1060, 730 cm^{-1}.

2-[2-(Benzyloxy)ethyl]furan 160

To a suspension of sodium hydride (4.30 g, 179 mmol) in 80 ml of THF at 0°C was added 156 (11.91 g, 106 mmol) in 40 ml of THF. After stirring for 30 minutes, benzyl bromide (12.8 ml, 108 mmol) was added dropwise. The reaction mixture was stirred for 12 hrs and was then poured into ice water. The aqueous phase was extracted with ether. The extracts were combined, washed with water and brine, dried, and concentrated in vacuo. Distillation afforded 19.70 g (92%) of 160 (bp 100°C, 4 mm Hg). NMR ($CDCl_3$) δ 2.94 (t, 2 H, J = 7 Hz), 3.73 (t, 2 H, J = 7 Hz), 4.53 (s, 2 H), 6.06 (d, 1 H, J = 4 Hz), 6.22 - 6.34 (m, 1 H), 7.29 (s, 6 H). C-13 NMR 28.87, 68.28, 72.83, 105.87, 110.16, 127.52, 128.30, 138.32, 140.99, 153.02 ppm. IR (film) 3010, 2940, 1590, 1495, 1443, 1355, 1135, 1090, 995, 720 cm^{-1}.

5-[2-(Benzyloxy)ethyl]-2-furancarboxaldehyde 161

To a solution of N,N-dimethylformamide (3.87 ml, 50 mmol) in 10 ml of 1,2-dichloroethane at 0°C was added phosphorus oxychloride (4.60 ml, 49.5 mmol). After stirring for 20 minutes, furan 160 (10.0 g, 49.5 mmol) in 10 ml 1,2-dichloroethane was added. The reaction mixture was stirred for 1 hr at 0°C and then 4 hrs at room temperature. The reaction

mixture was then poured into ice water and was neutralized with sodium carbonate. The aqueous phase was extracted with ether. The extracts were combined, washed with water and brine, dried, and concentrated in vacuo. Chromatography on silica gel using 2:1 hexane/ether as solvent yielded 9.80 g (86%) of 161 as a colorless liquid. NMR ($CDCl_3$) δ 2.98 (t, 2 H, J = 7 Hz), 3.73 (t, 2 H, J = 7 Hz), 4.48 (s, 2 H), 6.27 (d, 1 H, J = 4 Hz), 7.12 (d, 1 H, J = 4 Hz), 7.25 (s, 5 H), 9.50 (s, 1 H). C-13 NMR 29.20, 67.18, 72.96, 109.71, 114.84, 122.97, 127.52, 128.30, 137.93, 151.98, 160.56, 176.82 ppm. IR (film) 2880, 1680, 1520, 1400, 1365, 1285, 1200, 1100, 1025, 800, 750, 700 cm^{-1}. High resolution mass spectrum for $C_{14}H_{14}O_3$ requires 230.09430; measured 230.09423.

2-[(2,5-Dimethoxyphenyl)methyl]-5-(2-hydroxyethyl)furan 162 and 2-[(2,5-dimethoxyphenyl)hydroxymethyl]-5-(2-hydroxyethyl)furan 164

Using the tandem alkylation-reduction procedure developed for 128, a mixture of 162 (minor) and 164 (major) was obtained from p-dimethoxybenzene (2.76 g, 20 mmol), aldehyde 161 (4.68 g, 20 mmol), and lithium wire (46 mmol). Recrystallization from ethyl acetate/hexane yielded 3.22 g (58%) of 164 (mp 99 - 100°C). MHz 300, NMR ($CDCl_3$) δ 1.65 - 2.04 (br s, 2 H), 2.87 (t, 2 H, J = 6.5 Hz), 3.76 (s, 3 H), 3.79 (s, 3 H), 3.86 (t, 2 H, J = 6.5 Hz), 5.95 (d, 2 H, J = 3 Hz), 6.01 (d, 1 H, J = 3 Hz), 6.82 - 6.87 (m, 2 H), 6.94 (d, 1 H, J = 3 Hz). C-13 NMR 31.67, 55.73, 56.19, 60.80, 65.74, 107.04, 107.88, 112.05, 113.61, 113.80, 130.39, 150.87, 152.82, 153.80, 154.45 ppm. IR ($CDCl_3$) 3600 - 3100 (br), 2930, 1495, 1455, 1270, 1220, 1180, 1045, 910 cm^{-1}.

Resubmitting the mixture of 162 and 164 to the reduction conditions (2 equivalents of lithium, 15 minutes) afforded 162. Chromatography on silica gel using 2:1 hexane/ethyl acetate provided a 63% yield of 162 as a colorless oil. MHz 300, NMR ($CDCl_3$) δ 1.88 (br s, 1 H), 2.83 (t, 2 H, J = 6.5 Hz), 3.72 (s, 3 H), 3.77 (s, 3 H), 3.82 (t, 2 H, J = 6.5 Hz), 3.90 (s, 2 H), 5.88 (d, 1 H, J = 3 Hz), 5.98 (d, 1 H, J = 3 Hz), 6.69 - 6.80 (m, 3 H). C-13 NMR 28.48, 31.67, 55.54, 56.12, 61.00, 106.78, 106.97, 111.72, 116.40, 128.04, 151.59, 153.02, 153.60 ppm. IR (film) 3640 - 3180 (br), 2950, 2840, 1500, 1220, 1045, 900, 720 cm^{-1}. High resolution mass spectrum for $C_{15}H_{18}O_4$ requires 262.12051; found 262.12040.

7-Carboxy-8-[(2,5-dimethoxyphenyl)methyl]-4,11-dioxatricyclo[6.2.1.$0^{1,6}$]-undecan-5-one 167

Cycloaddition of 162 (1.23 g, 4.69 mmol) with maleic anhydride (0.46 g, 4.70 mmol) was accomplished using the procedure developed for 129. After stirring for 3 days, the reaction mixture was filtered and washed with cold ether to yield 1.29 g (75%) of crude 165.

Using the procedure developed for 130, the crude adduct 165 (1.29 g, 3.58 mmol) in 75 ml of THF was hydrogenated to afford 167. Recrystallization from acetone yielded 1.03 g (80%) of 167 (mp 256 - 257°C). The overall yield of 167 from 162 was 60%. Due to the insolubility of acid 167, it was esterified with diazomethane and was characterized as the methyl ester (mp 170 - 171°C). MHz 300, NMR ($CDCl_3$) δ 1.50 - 1.71 (m, 4 H), 2.08 - 2.22 (m, 2 H), 2.90 (d, 1 H, J = 14.3 Hz),

2.95 (d, 1 H, J = 9.4 Hz), 3.25 (d, 1 H, J = 14.3 Hz), 3.47 (d, 1 H, J = 9.4 Hz), 3.73 (s, 3 H), 3.76 and 3.77 (2 s, 6 H), 4.39 - 4.44 (m, 1 H), 4.79 - 4.82 (m, 1 H), 6.75 - 6.80 (m, 2 H), 6.92 (d, 1 H, J = 3 Hz). C-13 NMR 20.10, 30.48, 32.24, 36.17, 51.34, 51.87, 55.65, 55.88, 58.82, 66.00, 82.05, 88.26, 111.27, 112.46, 117.78, 125.95, 151.78, 153.20, 171.36, 171.50 ppm. IR ($CDCl_3$) 2980, 2860, 1735, 1720 (sh), 1505, 1470, 1435, 1365, 1270, 1230, 1050 cm^{-1}. Elemental analysis calculated for $C_{19}H_{22}O_7$ 167: C, 62.98; H, 6.12. Found: C, 62.95; H, 6.11.

8,11-Dimethoxy-1,12-dioxo-2-oxa-1,2,3,4,4a,5,6,6a,7,12,12a,12b-dodecahydro-4a,6a-epoxybenz[a]anthracene 168

To a suspension of 167 (0.526 g, 1.45 mmol) in 14 ml of dichloromethane at 0°C was added trifluoroacetic anhydride (0.43 ml, 3.04 mmol). The mixture was stirred for 30 minutes. Tin tetrachloride (0.51 ml, 4.36 mmol) was added at 0°C. The reaction mixture was stirred for 2 hrs at 0°C and then for 5 hrs at room temperature. The reaction mixture was poured into ice water and was extracted with dichloromethane. The extracts were combined, washed with brine, dried, and concentrated in vacuo. The residue was dissolved in chloroform and was filtered through silica gel to afford 0.424 g (85%) of 168 (mp 230 - 233°C). MHz 300, NMR ($CDCl_3$) δ 1.60 - 1.73 (m, 2 H), 1.97 - 2.20 (m, 4 H), 2.88 (d, 1 H, J = 7.8 Hz), 3.21 (d, 1 H, J = 20 Hz), 3.38 (d, 1 H, J = 20 Hz), 3.62 (d, 1 H, J = 7.8 Hz), 3.79 (s, 3 H), 3.82 (s, 3 H), 4.30 - 4.38 (m, 2 H), 6.78 (d, 1 H, J = 9 Hz), 6.95

(d, 1 H, J = 9 Hz. C-13 NMR 28.26, 28.73, 35.65, 36.50, 48.01, 55.88, 56.32, 61.16, 65.25, 84.23, 85.23, 110.18, 114.64, 122.60, 129.11, 149.94, 152.59, 172.40, 194.85 ppm. IR ($CDCl_3$) 2950, 1700, 1590, 1475, 1385, 1260, 1235, 1080, 970 cm^{-1}. Elemental analysis calculated for $C_{19}H_{20}O_6$: C, 66.27; H, 5.85. Found: C, 64.96; H, 5.94.

8,11-Dimethoxy-12-hydroxy-2-oxa-1-oxo-1,2,3,4,5,6-hexahydrobenz[a]-anthracene 169

To a solution of 168 (0.226 g, 0.66 mmol) in 5 ml of dichloromethane at 0°C was added boron trifluoride etherate (0.09 ml, 0.73 mmol). The reaction mixture was stirred for 20 hrs at room temperature and was then poured into ice water. The aqueous phase was extracted with dichloromethane. The extracts were combined, washed with water, dried, and concentrated in vacuo. Chromatography on silica gel using 2:1 chloroform/hexane as solvent afforded 0.144 g (67%) of 169 (mp 155 - 158°C). MHz 300, NMR ($CDCl_3$) δ 2.36 (t, 2 H, J = 7 Hz), 2.57 (t, 2 H, J = 7 Hz), 2.81 (t, 2 H, J = 7 Hz), 3.87 (s, 3 H), 3.92 (s, 3 H), 4.37 (t, 2 H, J = 7 Hz), 6.56 (s, 2 H), 7.47 (s, 1 H), 9.94 (s, 1 H). C-13 NMR 28.75, 29.05, 30.17, 55.63, 56.15, 64.96, 103.15, 103.60, 110.44, 113.97, 115.06, 124.15, 127.22, 136.77, 149.58, 149.77, 150.36, 154.13, 162.21 ppm. IR ($CDCl_3$) 3350, 3060, 2945, 1720, 1610, 1500, 1360, 1145, 1100, 1070 cm^{-1}. MS (m/e) 326, 311, 296, 282, 267, 253. Elemental analysis calculated for $C_{19}H_{18}O_5$: C, 69.93; H, 5.56. Found: C, 70.05; H, 5.60.

General procedure for oxidative-demethylation of para-dimethoxy aryl ethers

To a mixture of the dimethoxyaryl ether (1 mmol) and silver (II) oxide (4 mmol) in 10 ml of THF was added 6N HNO_3 (1.0 ml). The reaction mixture was stirred for 5 minutes and was then poured into water. The aqueous phase was extracted with chloroform. The extracts were combined, washed with water, dried, and concentrated in vacuo.

a. Quinones 170 and 171 NMR ($CDCl_3$ δ 2.46 - 2.88 (m), 3.95 (s), 4.49 (t, J = 6 Hz), 7.27 (d, J = 3 Hz), 12.26 (s), 12.50 (s). IR ($CDCl_3$) 3400 - 3000 (br), 2940, 1720, 1600, 1445, 1390, 1255, 1205, 1145 cm^{-1}. MS (m/e) 340 and 310.

b. Quinone 172 MHz 300, NMR ($CDCl_3$) δ 1.86 - 2.20 (m), 3.02 (d, J = 19 Hz), 3.04 (d, J = 7 Hz), 3.26 (d, J = 19 Hz), 3.57 (d, J = 7 Hz), 4.20 - 4.38 (m), 6.73 (d, J = 10 Hz), 6.85 (d, J = 10 Hz). IR ($CDCl_3$) 1710, 1655, 1460, 1380, 1280, 1260, 1050 cm^{-1}.

c. Quinone 178 MHz 300, NMR ($CDCl_3$) δ 1.78 - 2.22 (m), 3.06 (d, J = 8 Hz), 3.19 (d, J = 21 Hz), 3.39 (d, J = 21 Hz), 3.70 (d, J = 8 Hz), 4.24 - 4.35 (m), 7.69 - 7.77 (m), 8.02 - 8.11 (m).

2-[2-(Benzyloxy)ethyl]-5-[(1,4-dimethoxy-2-naphthalenyl)methyl]furan 174

To a solution of 2-bromo-1,4-dimethoxynaphthalene (97) (3.60 g, 13.5 mmol) in 15 ml of ether at -78°C was added n-butyllithium (14.0 mmol). After stirring for 10 minutes, aldehyde 161 (3.10 g, 13.5 mmol) in 20 ml of ether was added. The reaction mixture was allowed to warm to room temperature and was stirred for 30 minutes. The reaction mixture was then poured into water and was extracted with ether. The extracts were combined, washed with water and brine, dried, and

concentrated in vacuo. The crude alcohol was dissolved in 20 ml of THF and was added to a solution of sodium borohydride (1.02 g, 27 mmol) in 20 ml of distilled diglyme at 0°C. Boron trifluoride etherate (8.3 ml, 67 mmol) was added dropwise to the reaction mixture. The reaction mixture was stirred for 10 hrs and was then carefully quenched with water at 0°C. The aqueous phase was extracted with ether. The extracts were combined, washed with water and brine, dried, and concentrated in vacuo. Chromatography on silica gel using 8:1 hexane/ether afforded 2.98 g (55%) of 174 as a colorless oil. MHz 300, NMR ($CDCl_3$) δ 2.92 (t, 2 H, J = 6.2 Hz), 3.71 (t, 2 H, J = 6.2 Hz), 3.88 (s, 3 H), 3.91 (s, 3 H), 4.12 (s, 2 H), 4.50 (s, 2 H), 5.91 (d, 1 H, J = 3 Hz), 5.99 (d, 1 H, J = 3 Hz), 6.64 (s, 1 H), 7.30 (s, 5 H), 7.42 - 7.57 (m, 2 H), 8.04 (d, 1 H, J = 8 Hz), 8.21 (d, 1 H, J = 8 Hz). C-13 NMR 28.66, 29.05, 55.64, 62.35, 68.45, 72.95, 105.72, 106.67, 106.96, 121.90, 122.32, 125.08, 125.84, 125.98, 126.44, 126.53, 127.59, 128.37, 128.62, 138.31, 147.07, 151.83, 152.96 ppm. IR (film) 3050, 2940, 2860, 1600, 1460, 1365, 1260, 1220, 1085, 1000, 750 cm^{-1}. High resolution mass spectrum for $C_{26}H_{26}O_4$ requires 402.18312; measured 402.18256.

2-[(1,4-Dimethoxy-2-naphthalenyl)methyl]-5-[2-(hydroxy)ethyl]furan 157

To a suspension of activated 10% Pd/C (0.22 g) in 10 ml of ethanol under a hydrogen atmosphere was added 174 (2.25 g, 5.60 mmol) in 20 ml of ethanol. The reaction mixture was stirred for 8 hrs, filtered through celite, and concentrated in vacuo. Chromatography on silica gel using 1:1 hexane/ether yielded 1.62 g (93%) of 157 as a colorless oil. MHz 300, NMR ($CDCl_3$) δ 1.65 (br s, 1 H), 2.85 (t, 2 H, J = 6.2 Hz), 3.83

(t, 2 H, J = 6.2 Hz), 3.89 (s, 3 H), 3.93 (s, 3 H), 4.13 (s, 2 H), 5.91 (d, 1 H, J = 3 Hz), 6.00 (d, 1 H, J = 3 Hz), 6.63 (s, 1 H), 7.45 - 7.53 (m, 2 H), 8.04 (d, 1 H, J = 8 Hz), 8.20 (d, 1 H, J = 8 Hz). C-13 NMR 28.76, 31.77, 55.68, 61.21, 62.35, 105.63, 106.96, 107.28, 121.89, 122.27, 122.34, 125.14, 125.80, 126.60, 128.64, 147.11, 151.59, 151.87, 153.51 ppm. IR (film) 3700 - 3200 (br), 2960, 1600, 1560, 1375, 1265, 1220, 1090, 1000 cm^{-1}. High resolution mass spectrum for $C_{19}H_{20}O_4$ requires 312.13616; measured 312.13541.

7-Carboxy-8-[(1,4-dimethoxy-2-naphthalenyl)methyl]-4,11-dioxatricyclo-[6.2.1.$0^{1,6}$]undec-9-en-5-one 175

Cycloaddition of 157 (1.50 g, 4.80 mmol) with maleic anhydride (0.47 g, 4.80 mmol) was accomplished using the procedure developed for 129. After stirring for 4 days, the yellow gel was dissolved in ether. With rapid stirring, hexane was added dropwise. The solid was filtered and washed with cold ether to yield 1.20 g (60%) of crude 175. MHz 300, NMR ($CDCl_3$) δ 2.32 - 2.44 (m, 2 H), 2.87 (d, 1 H, J = 8.7 Hz), 3.28 (d, 1 H, J = 8.7 Hz), 3.30 (d, 1 H, J = 14.4 Hz), 3.65 (d, 1 H, J = 14.4 Hz), 4.43 - 4.51 (m, 1 H), 4.73 - 4.82 (m, 1 H), 6.21 (d, 1 H, J = 5.7 Hz), 2.26 (d, 1 H, J = 5.7 Hz), 6.79 (s, 1 H), 7.42 - 7.54 (m, 2 H), 8.02 (d, 1 H, J = 8.4 Hz), 8.19 (d, 1 H, J = 8.4 Hz).

The filtrate was concentrated in vacuo. The residue (0.71 g) was dissolved in 20 ml of methanol. After the addition of lithium hydroxide (0.30 g), the solution was refluxed for 12 hrs. The solution was then concentrated and diluted with water. The aqueous phase was

extracted with ether. The extracts were combined, washed with water and brine, dried, and concentrated *in vacuo*. Chromatography on silica gel using 1:1 hexane/ether afforded 0.37 g of 157.

7-Carboxy-8-[(1,4-dimethoxy-2-naphthalenyl)methyl]-4,11-dioxatricyclo-[6.2.1.$0^{1,6}$]undecan-9-one 158

Using the procedure developed for 130, the crude adduct 175 (1.20 g, 2.93 mmol) in 30 ml of acetone was hydrogenated to afford 1.14 g (95%) of 175 (mp 138 - 145°C) as a mixture of diastereomers. MHz 300, NMR ($CDCl_3$) δ 1.47 - 1.61 (m, 4 H), 2.14 - 2.22 (m, 2 H), 3.02 (d, 1 H, J = 9.2 Hz), 3.30 (d, 1 H, J = 14 Hz), 3.45 (d, 1 H, J = 14 Hz), 3.55 (d, 1 H, J = 9.2 Hz), 3.85 (s, 3 H), 3.95 (s, 3 H), 4.41 - 4.45 (m, 1 H), 4.80 - 4.84 (m, 1 H), 6.90 (s, 1 H), 7.45 - 7.54 (m, 2 H), 8.01 (d, 1 H, J = 7.9 Hz), 8.20 (d, 1 H, J = 7.9 Hz). C-13 NMR 28.06, 31.00, 32.42, 36.14, 51.19, 55.68, 58.90, 61.99, 65.82, 66.15, 82.29, 88.50, 106.70, 121.87, 122.20, 124.75, 125.05, 125.81, 126.37, 128.20, 147.51, 151.36, 172.40, 174.52 ppm. IR ($CDCl_3$) 3400 - 2820 (br), 1730, 1600, 1465, 1372, 1265, 1230, 1160, 1090 cm^{-1}. Elemental analysis calculated for $C_{23}H_{24}O_7$: C, 66.98; H, 5.87. Found: C, 64.70; H, 6.50.

8,13-Dimethoxy-1,14-dioxo-2-oxa-1,2,3,4,4a,5,6,6a,7,14,14a,14b-dodeca-hydro-4a,6a-epoxybenz[a]naphthacene 177

Using the procedure developed for 168, acid 158 (0.627 g, 1.52 mmol) was converted to ketolactone 177. Recrystallization from acetone/hexane afforded 0.45 g (75%) of 177 (mp 208 - 210°C). MHz 300,

NMR ($CDCl_3$) δ 2.05 - 2.19 (m, 4 H), 3.02 (d, 1 H, J = 8 Hz), 3.46 (d, 1 H, J = 18.9 Hz), 3.65 (d, 1 H, J = 18.9 Hz), 3.66 (d, 1 H, J = 8 Hz), 3.92 (s, 3 H), 3.98 (s, 3 H), 4.32 - 4.36 (m, 2 H), 7.52 (t, 1 H, J = 7 Hz), 7.61 (t, 1 H, J = Hz), 8.04 (d, 1 H, J = 8.2 Hz), 8.27 (d, 1 H, J = 8.2 Hz). C-13 NMR 28.20, 28.75, 35.98, 36.54, 49.34, 61.20, 61.37, 63.95, 65.42, 84.26, 85.49, 121.78, 122.01, 124.61, 125.68, 126.20, 128.53, 128.60, 130.89, 148.42, 153.82, 171.50, 195.44 ppm. IR ($CDCl_3$) 2960, 1715, 1615, 1450, 1375, 1340, 1270, 1080, 1035 cm^{-1}. Elemental analysis calculated for $C_{23}H_{22}O_6$: C, 70.04; H, 5.62. Found C, 69.90; H, 5.69.

4a,14-Dihydroxy-2-oxa-1,8,13-trioxo-1,2,3,4,4a,5,6,8,13,14b-decahydro-benz[a]naphthacene 179

Using the general oxidative-demethylation procedure, ketolactone 177 (0.083 g, 0.21 mmol) was oxidized to quinone 178. The crude quinone was dissolved in 5 ml of acetone. After the addition of concentrated HCl (1 drop), the reaction mixture was stirred for 20 hrs. The yellow precipitate was filtered and washed with cold acetone to afford 0.023 g (30%) of 179 (mp 263 - 268°C) as a mixture of diastereomers. MHz 300, NMR (d_6-DMSO) δ 1.99 - 2.48 (m, 4 H), 4.19 and 5.12 (two s, 1 H), 4.43 - 4.64 (m, 2 H), 7.53 (s, 1 H), 7.92 - 7.98 (m, 2 H), 8.18 - 8.26 (m, 2 H), 13.01 (s, 1 H). MS (m/e) 364, 346, 316, 302, 292, 275, 263. High resolution mass spectrum for $C_{21}H_{16}O_6$ requires 364.0947; found 364.0960.

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ACKNOWLEDGEMENTS

"You can't always get what you want."

Mick Jagger and Keith Richards,

The Rolling Stones

I would like to thank Dr. Kraus for his steadfast guidance and continuous enthusiasm throughout this project. I also want to thank Mrs. Lynn Moore for typing this manuscript and for her diligence in doing so.

Secondly, I would like to thank my parents for their support and encouragement during the last 5 years. I would also like to thank my late grandmother, Mrs. Raymond Ward, and my late grandfather, Mr. Oscar Hagen, for their support and encouragement during my undergraduate education.

Finally, I want to thank the members of Kraus' group and all my friends at Iowa State University for their friendship, especially Steve Crowley for his guidance during my early years of research, Brian Fulton for being himself, and Susan Prugh for her everlasting friendship and support.