TOTAL SYNTHESIS OF O-METHYL KIDAMYCINONE

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DEDICATION

To my late father

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ABSTRACT

Two new efficient methods for the regiospecific construction of functionalized aromatic rings have been developed. The new ring annelation methodology involves respective condensation of the anion of ethyl 2-phenylsulfinylmethylbenzoate and 3-phenylsulfonyl-1(3H)-isobenzofuranone with various Michael acceptors to give initial adducts. The resulting adducts are then in situ cyclized and aromatized, then methylated to furnish regiospecifically constructed, selectively protected 1-hydroxy-2,3-disubstituted naphthalenes and 1,4-dimethoxy-2,3-disubstituted naphthalenes, respectively.

In order to demonstrate the efficacy of this new synthetic methodology, synthesis of methyl kidamycinone, the aglycone of O-methyl ether of antitumor antibiotic kidamycin was accomplished. The synthesis of O-methylkidamycinone consists of two major stages; 1) initial regiospecific construction of an anthracene intermediate possessing an ortho-hydroxyl and acetyl functional groups using the newly developed ring annelation methods, and 2) subsequent formation of the pyrone moiety utilizing the ortho-hydroxyl and acetyl functionalities present in the anthracene intermediate.

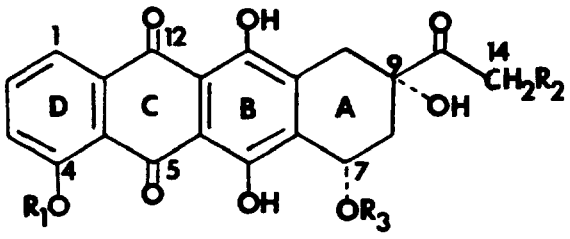
I. INTRODUCTION

In recent years, a large number of sugar substituted compounds with linear polynuclear aromatic systems have been isolated.[1-13] The aromatic portion, forming the key structural feature of these compounds, consists of two or three polyhydroxy aromatic rings joined with a functionalized alicyclic moiety or, in certain cases, with other complex functionalities.

In addition to their significant antibiotic activity, they frequently exhibit potent antineoplastic activity against a variety of expermental tumors as well as certain types of human cancers.

Leading examples of these compounds are the anthracycline antibiotics adriamycin,[1] daunorubicin,[2] and carminomycin,[3] which possess tetrycyclic ring systems, olivomycin A, B, C, and D,[4] chromomycin A1-4[4a,5] and aureolic acid,[6] which possess a naphthacycline nucleus, and kidamycin,[7] hedamycin,[8] indomycin,[9] pluramycin A,[10] neopluramycin,[10a] which have tricyclic anthraquinone ring systems with an attached 2-substituted pyrone nucleus.

Among these numerous polynuclear aromatic antibiotics, the anthracyclines adriamycin (1a) and daunorubicin (2a) are currently the most widely used for cancer treatments. Adriamycin which has an especially broad spectrum of activity has received the most attention.[14]

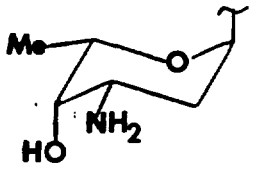


1a Adriamycin

R_1=Me, R_2=OH, R_3= daunosamine

1b Adriamycinone

R_1=Me, R_2=OH, R_3=H



R_3

2a Daunorubicin

R_1=Me, R_2=H, R_3= daunosamine

2b Daunomycinone

R_1=Me, R_2=R_3=H

The remarkable efficacy of these antineoplastic agents and their inefficient production by fermentation processes[15] has greatly stimulated efforts to develop efficient synthetic methodology for the production of the aglycones.

Although numerous synthetic procedures have appeared in the literature in connection with the search for a general, effective route to the preparation of linear polynuclear aromatic systems, studies have, for the most part, focused on the anthracyclinones, the tetracyclic system of anthracycline antibiotics. The most frequently employed methodology for constructing the tetracyclic skeleton has been the

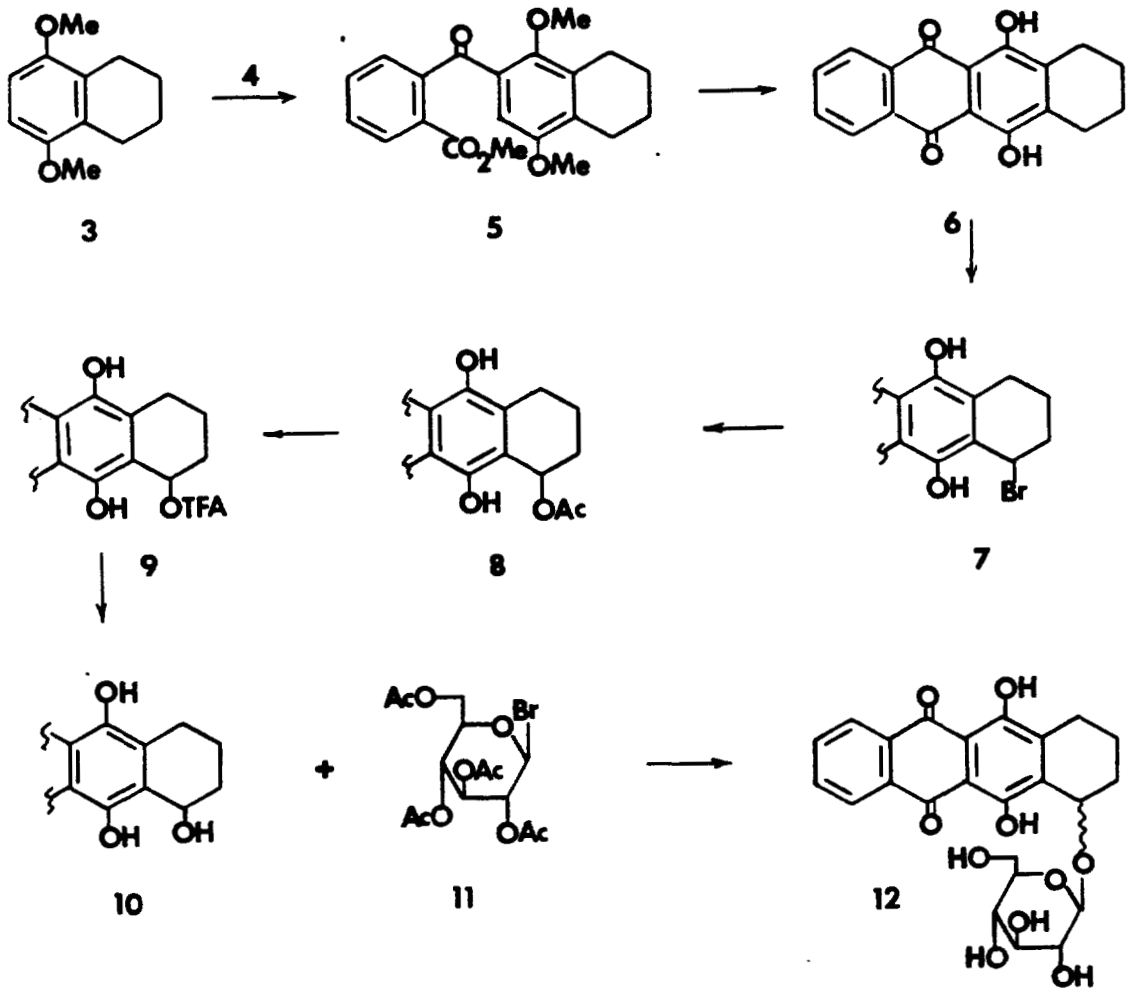
use of (A) the Friedel-Crafts reaction,[16] (B) variant forms of Diels-Alder reaction,[17] or (C) the Fries rearrangement.[18] With a few exceptions,[17g, 18, 19] most of these methods suffer from a lack of regiospecificity in forming the tetracyclic skeleton with the proper orientation of A and D-ring substituents. In addition, the reported regiospecific approaches have an apparent limitation in that they are unadaptable for large scale preparation. Furthermore, they are not applicable to the preparation of polynuclear aromatic systems devoid of quinone moieties.

The major part of the work to be described in this thesis is aimed at the development of an efficient, regiospecific synthetic methodology for the preparation of the linear polynuclear aromatic systems. Since this work is closely related to the synthesis of anthracyclinones, some of the synthetic procedures that have appeared in the literature for the preparation of these compounds will be reviewed in this section.

A. Friedel-Crafts Acylation Route

The first synthesis of a tetracyclic analog of daunomycinone (2b) was reported by Goodman et. al. in 1968,[16a] who prepared the model system 12 in order to establish structure-activity relationships for the parent antibiotic. The preparation of the analog was achieved utilizing a Friedel-Crafts acylation route (Scheme I-1). Condensation of dimethoxytetrahydronaphthalene 3 with the mixed anhydride of methyl hydrogen phthalate in the presence of trifluoroacetic

Scheme I-1

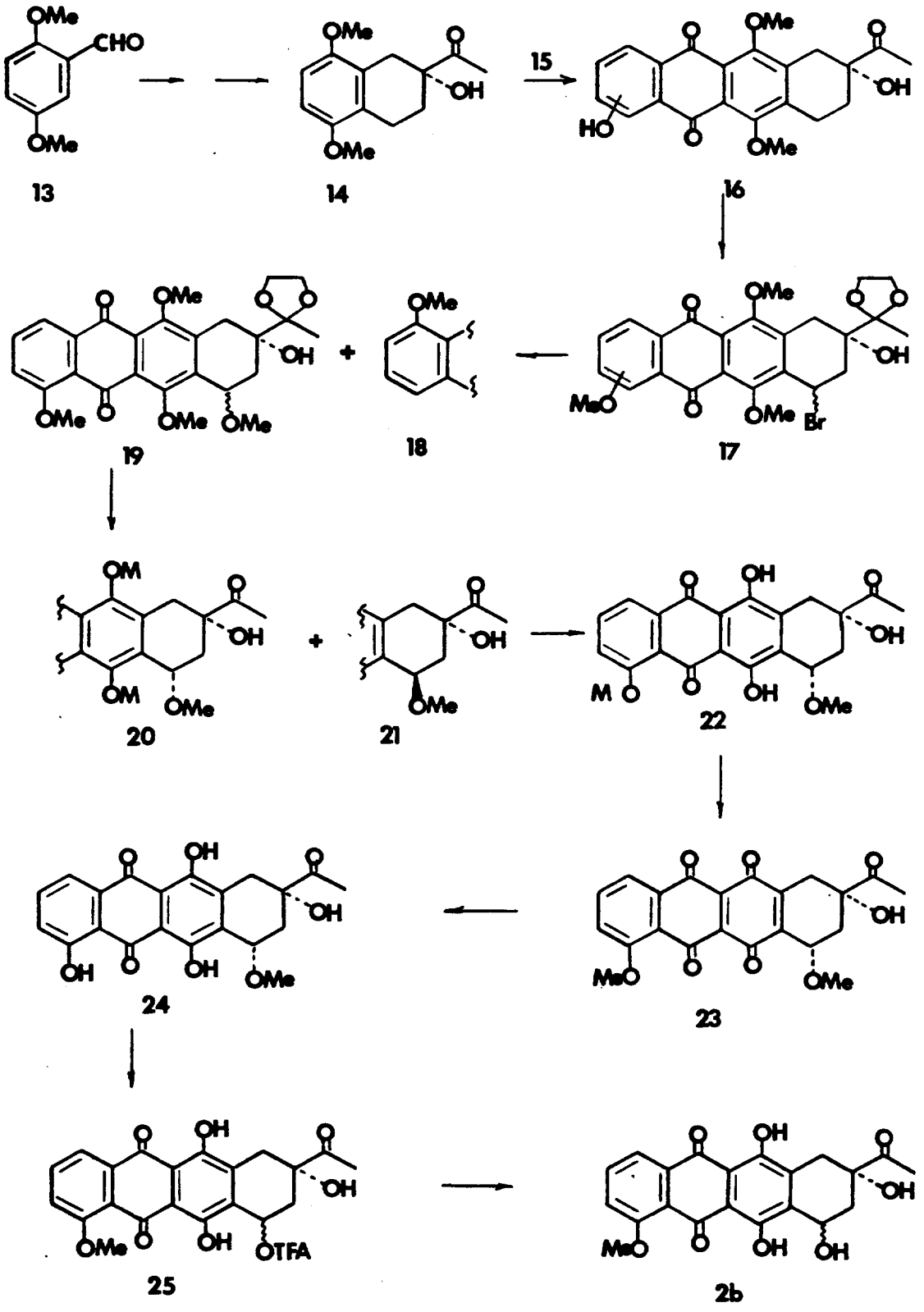


acid gave tricyclic keto ester 5. Saponification of 5, followed by acid cyclization of the resulting keto acid furnished, following demethylation of the cyclization product with aluminum chloride, tetracyclic hydroxy quinone 6. Benzylic bromination of 6 with trimethylammonium tribromide yielded bromo compound 7 which was transformed to 8 with silver acetate. Direct hydrolysis of acetoxy compound 8 failed to provide the model aglycone 10. The problem was overcome by converting 8 to trifluoroacetoxy compound 9, which was then smoothly hydrolyzed

to tetracyclic aglycone 10. Preparation of D-glucoside 12 was accomplished by condensing 10 with acetobromoglucose 11 in the presence of mercuric cyanide, followed by hydrolysis with sodium methoxide.

In 1973, Wong et. al. reported the first total chemical synthesis of daunomycinone (2b) (Scheme I-2).[16c] The construction of the tetracyclic ring skeleton utilized the ring annelation method developed by Goodman and his coworkers. The bicyclic ketol 14, prepared from dimethoxybenzaldehyde 13 in 7 steps, was condensed with 3-acetoxyphthalic acid monomethyl esters (isomeric mixture) (15) to yield a mixture of diaryl keto esters. Following saponification of the aryl keto ester, acylative cyclization was performed with liquid hydrogen fluoride to give a mixture of tetracyclic compounds 16 in 19% yield from 14. Separation of the ring-D isomers was not feasible at this stage. The mixture was converted to bromo compound 17 by initially protecting the aromatic phenolic functionality as a methyl ether and the side chain carbonyl group with a dioxolane group, followed by bromination at C-7 with N-bromosuccinimide. Methanolysis of the bromo compound 17 furnished a mixture of 7-methoxy compounds, which were finally separated by preparative thin layer chromotography to afford ring-D isomers 18 and 19. Removal of ketal functionality from 19 yielded ring-A isomers 20 and 21, which were also separated. Demethylation of tetramethoxy compound 19 with aluminum trichloride gave tetrahydroxy compound 22. Oxidation of 22 with lead tetraacetate furnished the unstable diquinone 23, which was immediately remethylated (Me_2SO_4/K_2CO_3) to furnish 24 in an overall yield of 10% from 19. Demethylation of the 7-methoxy functionality in 24 was not accomplished by a direct method. The compound was first

Scheme I-2


OMe
CHO
OMe
13
OMe
OH
OMe
14
15
OMe
OH
HO
OMe
16
OMe
OH
OMe
OMe
OMe
19
OMe
+
18
OMe
OH
MeO
OMe
Br
17
OM
OH
OM
OMe
20
+
OH
OMe
21
OH
OH
M O
OH
OMe
22
OH
OH
OH
OMe
24
OH
OH
MeO
OMe
23
OMe
OH
OTFA
25
OH
OH
MeO
OH
OH
2b

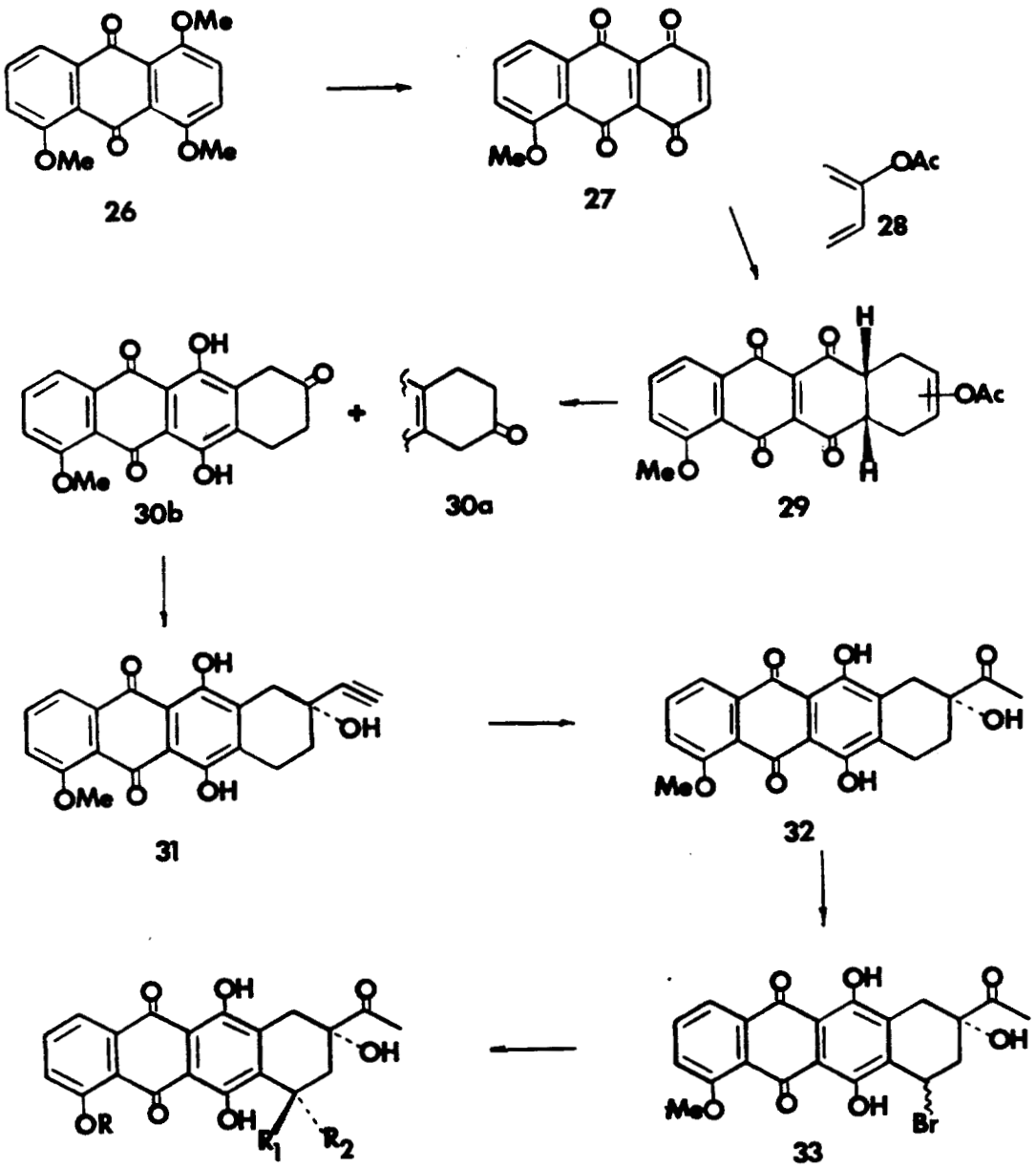
converted to trifluoroacetoxy compound 25 by treating with trifluoroacetic acid and then hydrolyzed with ammonium hydroxide to provide daunomycinone (2b) as a mixture of epimeric isomers.

B. Diels-Alder Route

A few years later, a more practical route for the large scale preparation of the aglycones of these antibiotics was introduced by Kende et.al.(Scheme I-3).[17a] This synthesis utilized a Diels-Alder reaction to construct the A-ring portion of the tetracyclic skeleton.

The starting material was 5-methoxy-1,4,9,10-anthradiquinone (27) (quinizarinone), readily available from trimethoxy anthraquinone 26.[20] Cycloaddition of 27 with 2-acetoxybutadiene (28) gave a 1:1 isomeric mixture of Diels-Alder adducts 25 in 71% yield. It is interesting to note that the electron-poor diene 27 produced the tetracyclic compound 29 by a terminal addition (2,3), whereas an electron-rich diene such as 2-ethoxybutadiene is known to give the internal addition (4a, 9a) product.[17a,21] Aromatization of 29 (NaOAc/HOAc), followed by hydrolysis (HCl/EtOH) of the enol acetoxy compound furnished a mixture of ketones 30a and 30b (1:1) in 85% yield. Condensation of 30b with ethynylmagnesium bromide gave a 52% yield of the ethynylcarbinol 31, which was hydrated with mercuric oxide in aqueous sulfuric acid (HgO/H_2SO_4) to furnish (±)7-deoxydaunomycinone (32) in 40% yield. Selective bromination at C-7 of compound 32 with bromine in carbon tetrachloride by irradiation with a sunlamp provided the labile bromo compound 33, which was hydrolyzed on moist silica gel to yield

Scheme I-3



34 R=Me, R_1=OH, R_2=H

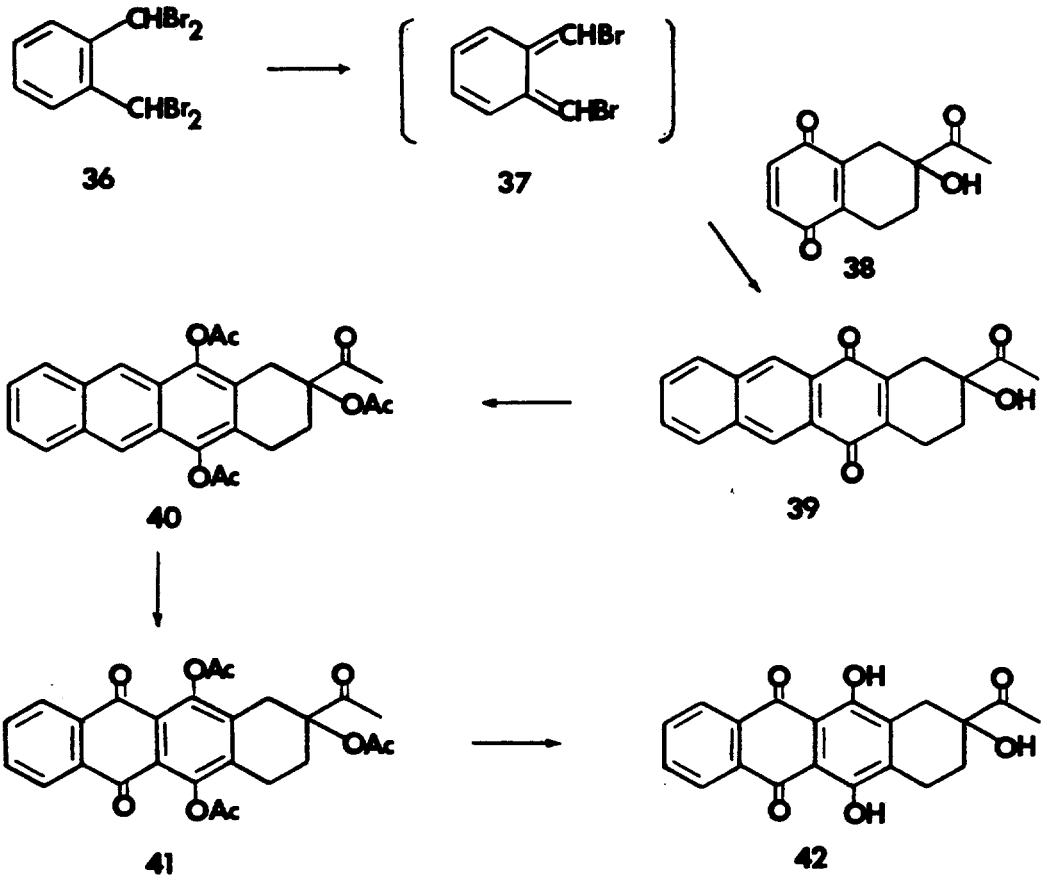
2b R=Me, R_1=H, R_2=OH(50%)

35 R=R_1=H, R_2=OH

(±)-daunomycinone (2b) and its epimer 34 in a 2:5 ratio. Epimerization of 34 to daunomycinone was accompolished in 75% yield by treating it with trifluoroacetic acid, followed by aqueous workup. The total yield of (±)-daunomycinone from 33 was ca 50%. Daunomycinone obtained here was converted to (±)-carminomycinone (35) upon demethylation with aluminum trichloride.

Recently, an alternative approach to the synthesis of tetracyclinones employing a different form of the Diels-Alder reaction was introduced by Wiseman et. al. (Scheme I-4).[17m] This method constructed the tetracyclic ring skeleton by trapping an o-quinodimethane 37 with an appropriately substituted quinone. Reaction of tetrabromoxylene (36)

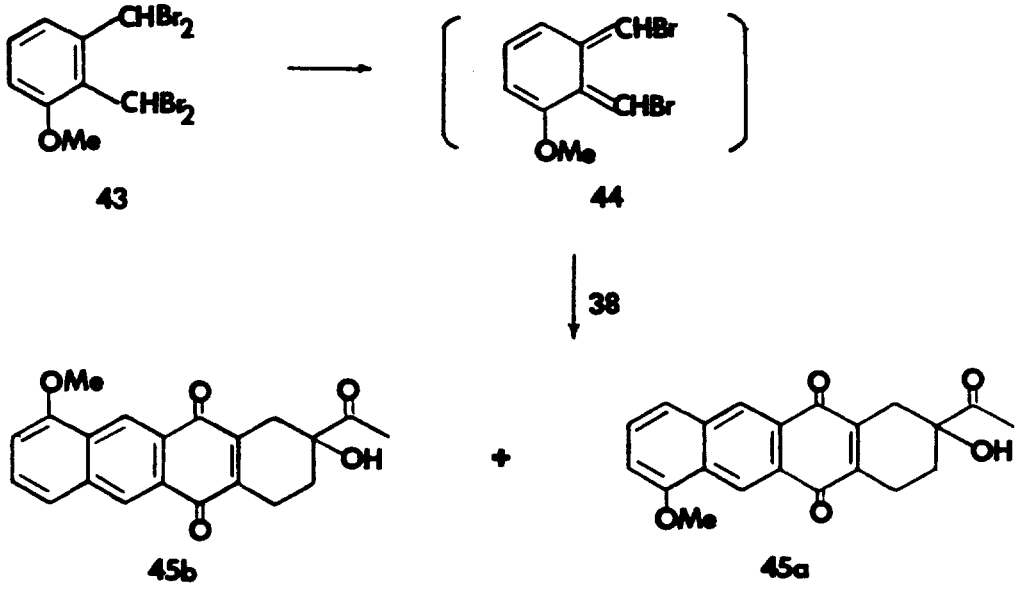
Scheme I-4



with sodium iodide in the presence of quinone 38 produced, with spontaneous loss of hydrogen bromide, tetracyclic compound 39 in 40% yield. Reductive acetylation of 39 (Zn, Et_3N, Ac_2O) afforded hydroquinone triacetate 40 (94%), which was oxidized with Jones reagent to 41 and hydrolyzed to 4-demethoxydaunomycinone analog 42 in 69% yield from 40.

The o-quinodimethane approach was extended to the synthesis of the methoxy series corresponding to daunomycinone. When 3-methoxytetrabromoxylene (43), prepared from 2,3-dimethylanisole by bromination with N-bromosuccinimide, was allowed to react with quinone 38 in the presence of sodium iodide, a mixture of two regioisomeric quinones 45a and 45b were produced (Scheme I-5).

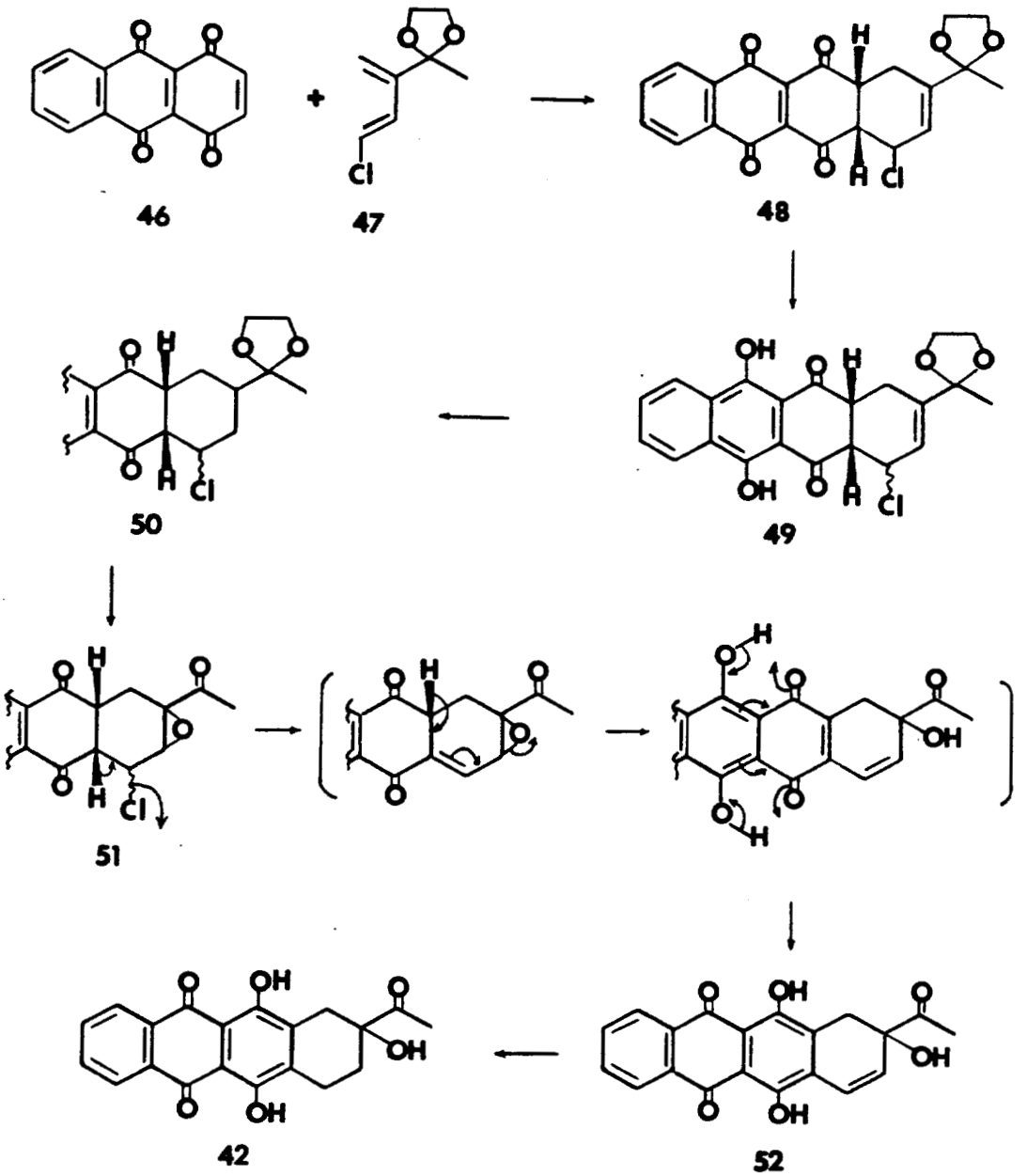
Scheme I-5



A more efficient route to 4-demethoxy-7-deoxydaunomycinone (42) was recently reported by Kelly and Tsang (Scheme I-6).[17n] Diels-

Alder reaction between diquinone 46[22] and chlorodiene 47 gave an 85% yield of adduct 48, which upon treatment with p-toluenethiol gave

Scheme I-6



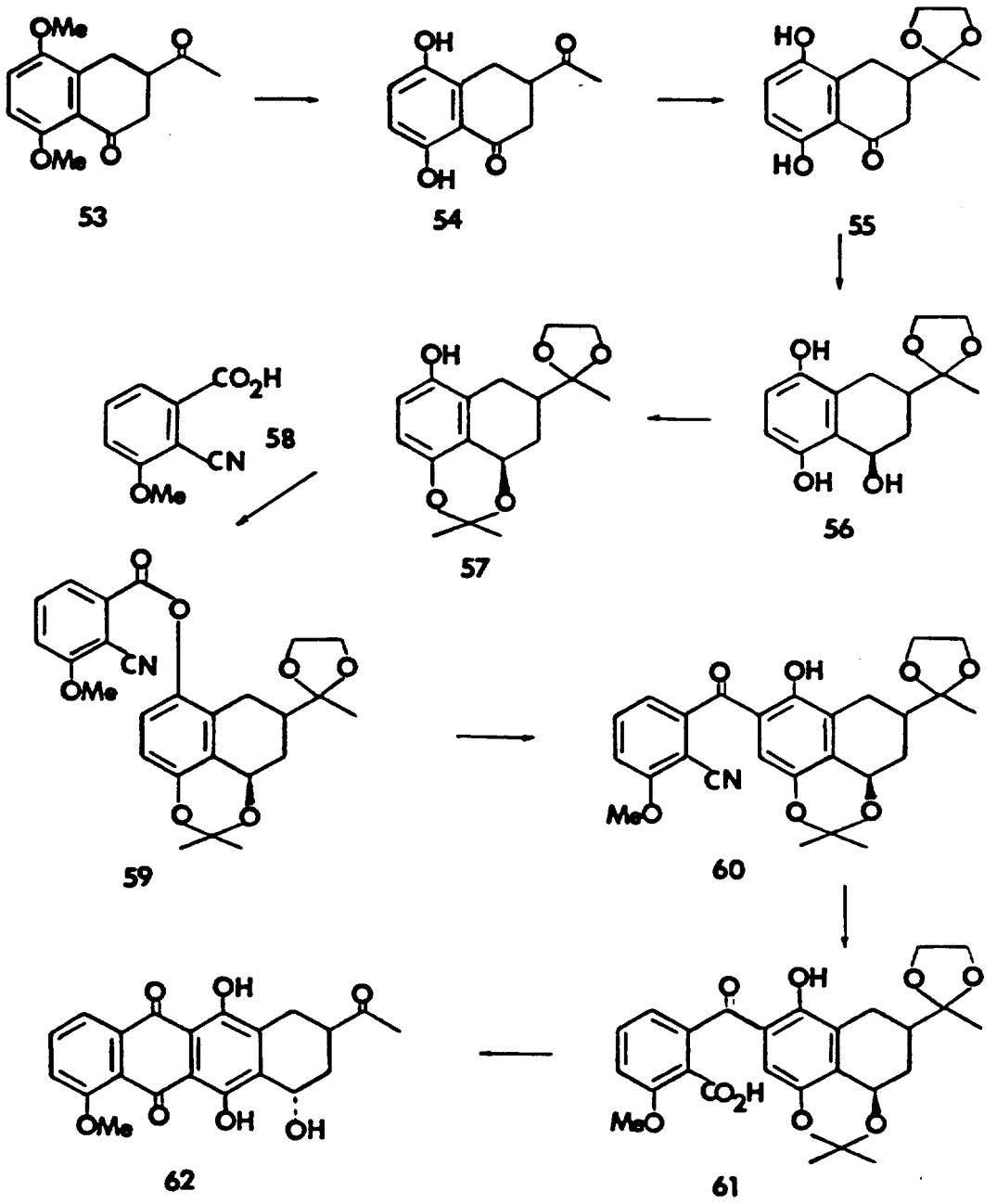
hydroquinone 49. Epoxidation of 49 to 50 was followed by elimination of HCl ($CF_3CO_2H/\emptyset NO_2$) to produce a compound which rearranged to 52 in 40% overall yield from 48. Catalytic hydrogenation of 52 furnished 4-demethoxydaunomycinone analog 42.

C. Fries Rearrangement Route

Preparation of the tetracyclic aglycone of anthracylcine antibiotics has also been accomplished by approaches utilizing the Fries rearrangement. Kende et. al.[18a] and Shi et. al.[18b] have synthesized daunomycinone analogues by this methodology. Especially noteable was the work of Kende and his coworkers since this synthetic procedure retained its regiospecificity (Scheme I-7).

The starting material, dimethoxytetralone 53, was prepared from 2,5-dimethoxybenzaldehyde in 5 steps by the method of Wong.[16b] Demethylation of the dimethyl ether 53 by boron tribromide yielded the dihydroxytetralone 54 (76%), which was transformed to 55 in 91% yield by selective ketalization. The ketal 55 upon reduction with sodium borohydride furnished trihydroxyketal 56. Treating 56 with 2,2-dimethoxypropane in the presence of p-toluenesulfonic acid gave the highly sensitive ketal acetonide 57 (88%). The photo-Fries precursor 59 was prepared in 77% yield by acylation of the free phenolic group of 57 with 2-cyano-3-methoxybenzoic acid (58) under basic conditions. The photo-Fries rearrangement of o-cyanobenzoate 59 was extremely critical and the reaction was carried out only to the half-disappearance of the starting material since over irradiation destroyed the resulting product. The rearrangement was accomplished by a direct irradiation

Scheme I-7



53 54 55 56 57 58 59 60 61 62

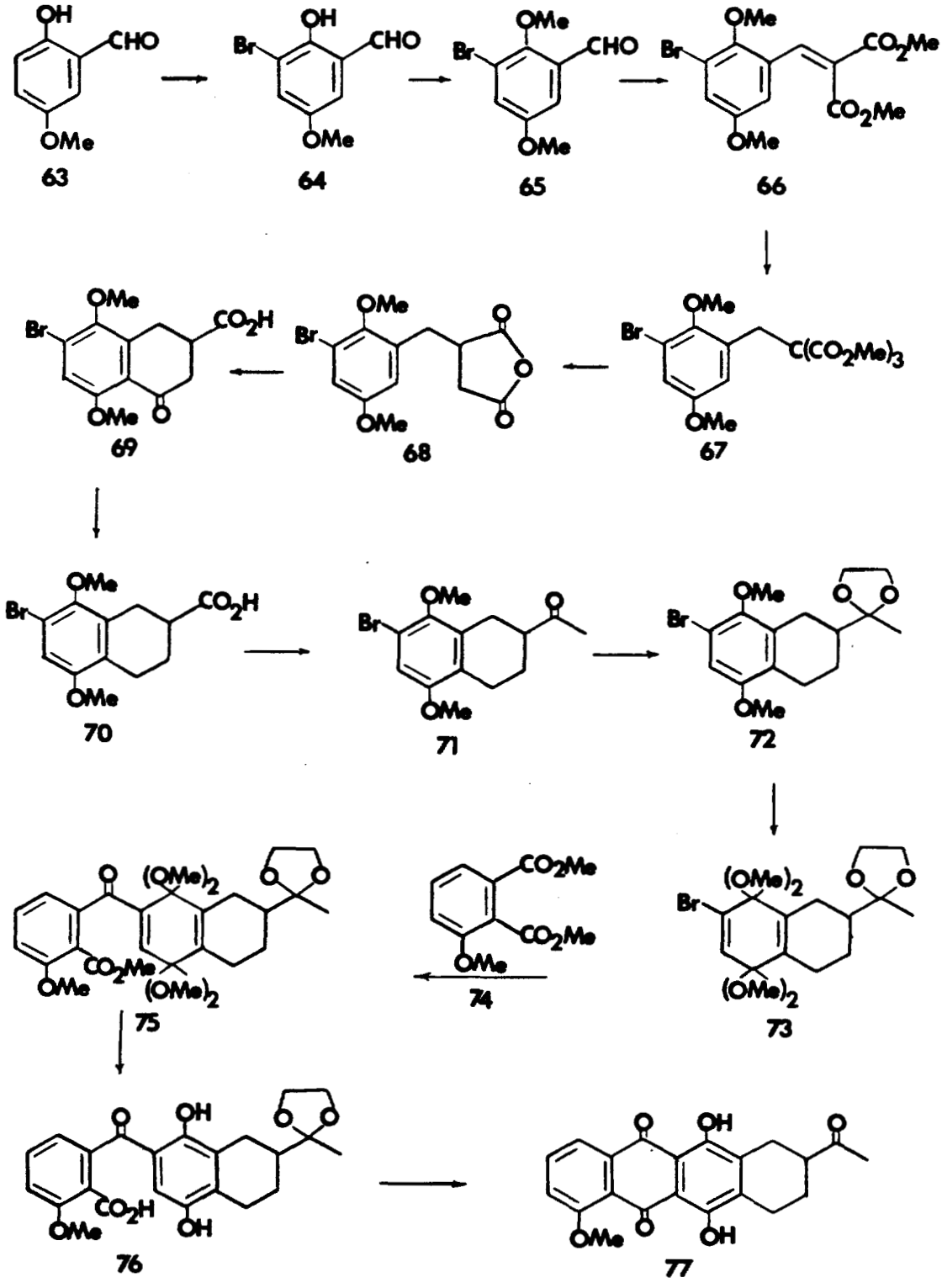
with a 450-w medium pressure Hanovia source using 1% solution of the compound in dry dioxane in a quartz vessel. The yield of the Fries product 60 was ca 48% on the basis of the starting material consumed. Hydrolysis of the hindered cyano function of 60 was accomplished in quantitative yield to give keto acid 61, which produced, upon treatment with liquid hydrogen fluoride (±)-9-deoxydaunomycinone 62 in 23% yield.

D. Miscellaneous Routes [19,23]

For preparaton of the aglycones of anthracycline antibiotics, regiospectific construction of the tetracyclic ring skeleton is essential. Numerous efforts have, therefore, been directed toward the regiospecific synthesis of the tetracyclinones. One of these efforts was the work of Swenton et. al.,[19] which accomplished an efficient synthesis of (±)-7,9-deoxydaunomycinone (77) from 3-bromo-2,5-dimethoxybenzaldehyde (65). The key step, regioselective construction of the tetracyclic ring skeleton was accomplished by reacting a latent quinone carbanion with a methoxy substituted phthalate diester (Scheme I-8).

The dimethoxybromobenzaldehyde 65 was prepared from 2-hydroxy-5-methoxybenzaldehyde 63 by bromination with Br_2/HOAc,[24] followed by methylation of the resulting product with dimethylsulfate and base. Knoevenagel condensation of benzaldehyde 65 with malonic ester produced the unsaturated diester 66, which was converted to triester 67 by reduction with lithium tri-sec-butylborohydride followed by in situ alkylation of the anion intermediate with methyl bromoacetate. Transformation of the triester 67 was achieved by basic hydrolysis of 67,

Scheme I-8


OH
CHO
OMe
63
Br
64
65
66
CO2Me
67
C(CO2Me)3
68
69
CO2H
70
71
72
73
(OMe)2
74
CO2Me
75
76
77

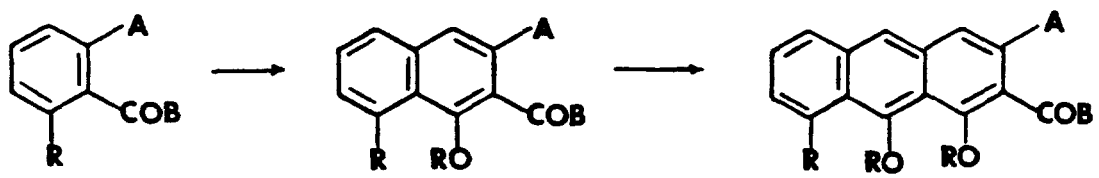
followed by treatment of the dicarboxylic acid with acetic anhydride. Cyclization of anhydride 68 with liquid hydrogen fluoride gave the bicyclic ketone 69. The presence of the carbonyl functionality in the alicyclic ring system was observed to generate complications in the subsequent reaction, giving ring-A aromatized product. Hence, the cyclic ketone function of 69 was removed by reduction with triethylsilane and trifluoroacetic acid to yield 70.[25] Carboxylic acid 70 was converted to ketone 71 by a three-step route involving esterification of the acid function with diazomethane, displacement of the methyl ester with the lithium salt of dimethylsulfoxide, and reductive cleavage of the sulfoxide functionality with aluminum amalgam. Protection of the side chain carbonyl function of 71 (ethylene glycol, p-toluenesulfonic acid) followed by anodic oxidation of the resulting ketal 72 produced the unstable latent quinone 73. The anion of 73, generated with n-BuLi, was reacted with dimethyl 3-methoxyphthalate 74 to give the regioselectively formed keto ester 75. Compound 75 was converted to keto acid 76 by hydrolysis of the quinone bisketal ($SnCl_2$, H_2SO_4), followed by saponification of the ester group with aqueous sodium hydroxide. Acid cyclization of 76 (HF or $MeSO_3H$) furnished 7,9-deoxydaunomycinone (77).

II. GENERAL SYNTHETIC STRATEGY FOR POLYNUCLEAR AROMATIC SYSTEMS

Over the years an enormous effort has been expended to develop efficient synthetic routes for the preparation of polynuclear aromatic systems. The majority of the routes suffer from a lack of regiospecificity and require tedious chromatographic separation of the resulting isomeric mixtures. Furthermore, the reported regiospecific or regioselective approaches are usually not adaptable for large scale preparations; moreover, they are not applicable to the preparation of polynuclear aromatic systems devoid of quinone moiety.

In an effort to overcome these problems the general synthetic strategy shown below was devised (Scheme II-1).[26] In this approach,

Scheme II-1



absolute regiochemical control over the regiochemistry of the products is vested in the starting benzoate system. The ortho-substituents A and COB are used to annelate a new aromatic ring, thereby controlling the position of attachment of the added ring. During the construction

process, new A and COB substituents are regioselectively built onto the newly formulated ring to permit further ring replications. Two executions yield an anthracene with regioselective placement of A and COB substituents.

The above synthetic strategy is potentially a solution to regiospecific construction of polynuclear aromatic systems. Advantages of the approach are:

1. an absolute control over isomer construction, and
2. manipulative control over each ring as it is constructed.

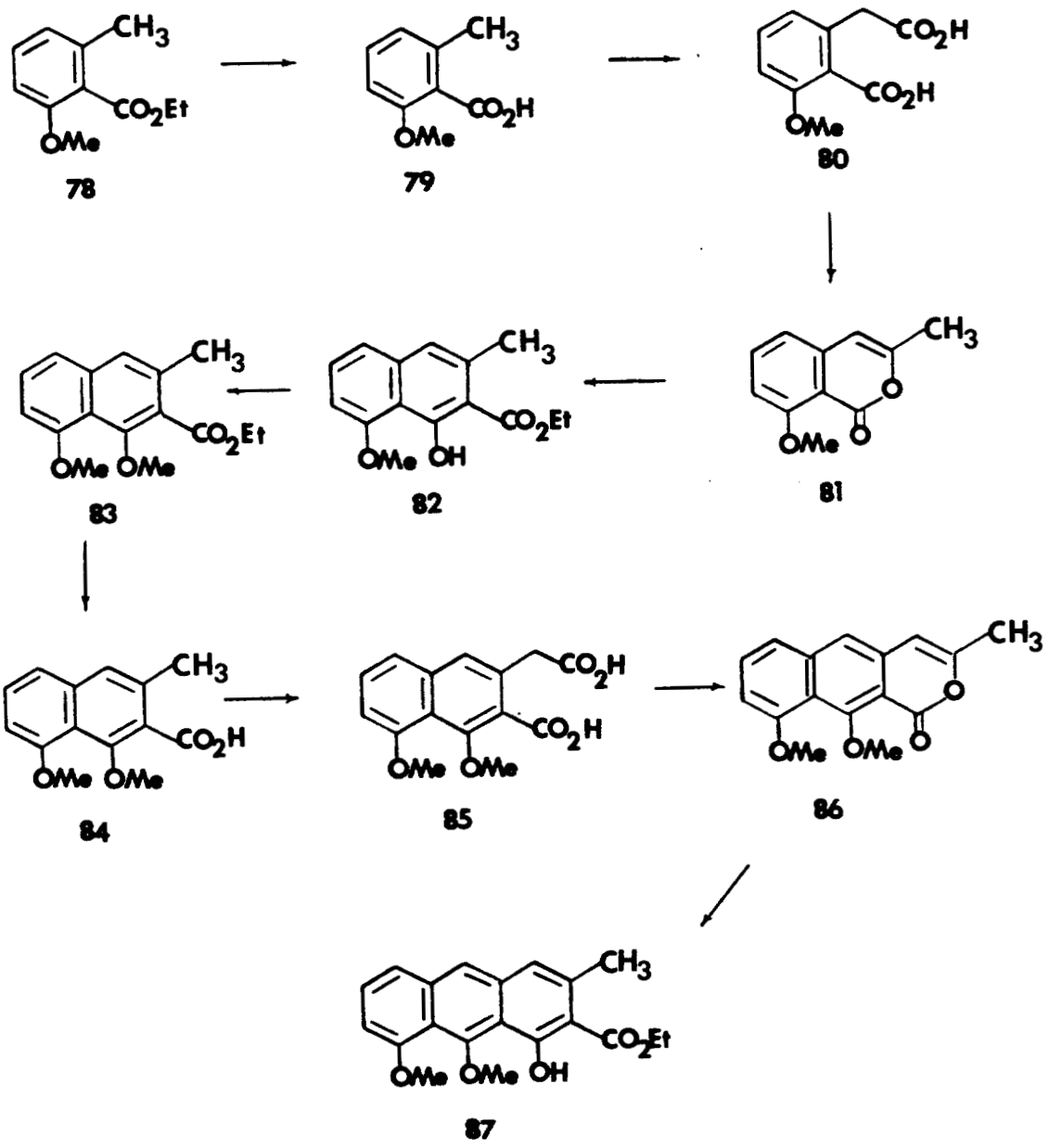
The newly formed phenolic ring can be oxidized to a quinone or selectively protected for further manipulation.

The numerous potential advantages attendant with the use of the strategy encouraged us to examine methods to accomplish it.

III. BACKGROUND OF CURRENT STUDY

The synthetic strategy presented in Section II was initially demonstrated by the conversion of ethyl 6-methoxy-2-methylbenzoate (78) to a polyfunctionalized anthracene carboxylic ester 87 through a two

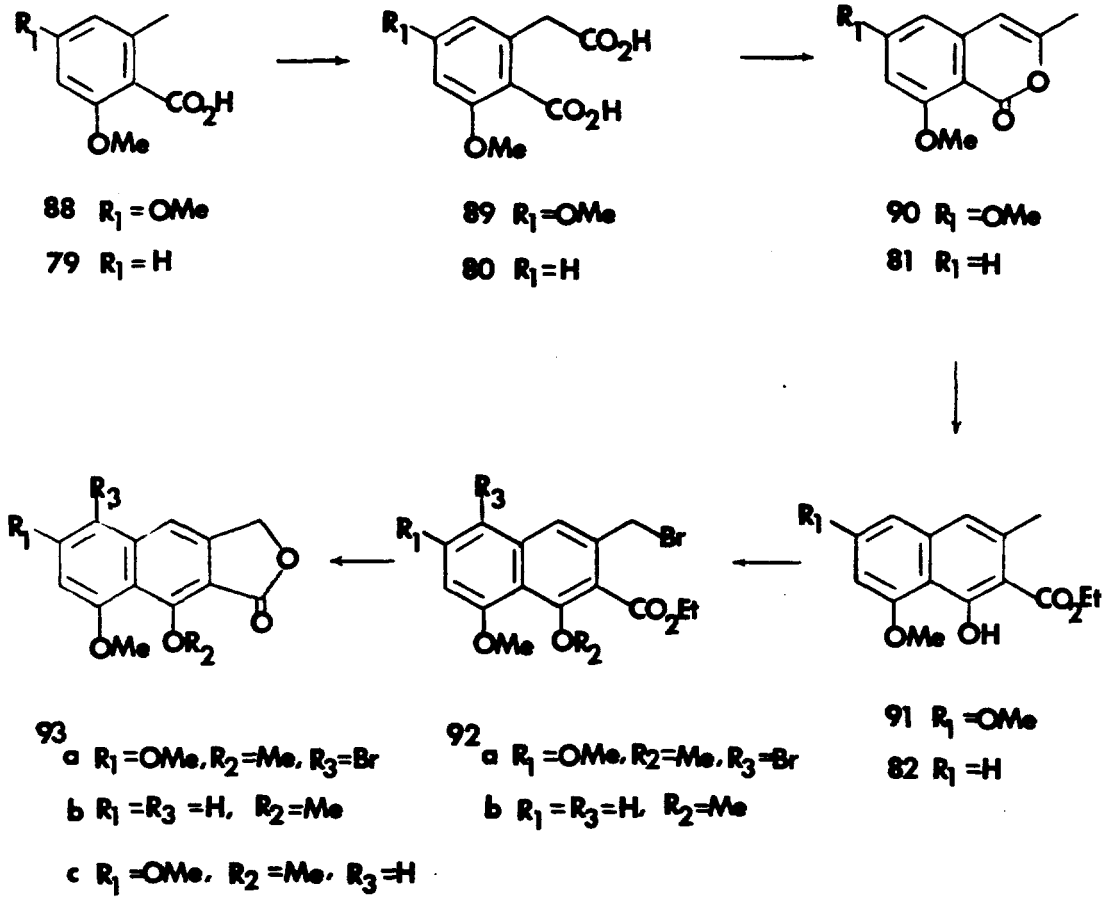
Scheme III-1



cycle reaction sequence (III-1).[26] The disubstituted benzoic acid 79[27] was obtained quantitatively by base hydrolysis of 78. Using a method developed by us, 79 was converted to a dilithium anion (lithium diisopropylamide, -78°C) then reacted with dimethyl carbonate.[28] Aqueous workup furnished directly 2-carboxy-3-methoxybenzeneacetic acid (80) (92%). Preparation of 8-methoxy-3-methyl-1H-2-benzopyran-1-one(81) from 80 was accomplished in 68% yield via a three-step reaction sequence. The sequence involved acylation of 80 with acetic anhydride in pyridine, followed by basic hydrolysis with concomitant decarboxylation, and finally dehydrative cyclization of the resulting keto acid using acetic anhydride in ethyl acetate with perchloric acid as a catalyst.[29] High dilution Reformatsky reaction of the reagent generated from ethyl bromoacetate with 81 furnished regioselectively functionalized naphthoate 82 in 73% yield.[30] The same pattern and functional groups are present in naphthoate 82 as were present in the starting material 78. Following methylation of 82 to give 83, a second annelation sequence was performed to convert 83 to anthracenecarboxylic ester 87.

The applicability of the synthetic strategy for natural products synthesis was demonstrated by performing abbreviated, regiospecific syntheses of the methyl ethers of the naturally occurring naphthalides α- and β-sorigenin (Scheme III-2).[31] The syntheses of these compounds were accomplished by parallel reaction sequences using dimethylorsellinic acid (88) and 6-methoxy-2-methylbenzoic acid (79) as the corresponding starting materials.[32] Conversion of 79 to 82 was described earlier in Scheme III-1. Transformation of dimethylorsellinic acid (88) to the

Scheme III-2



corresponding naphthoate 91 was accomplished by a sequence analogous to the preparation of 82. The yield of benzopyran 90 from 88 was comparable with that of 81 obtained from the monomethoxylated compound 79. Reformatsky reaction of ethyl bromoacetate with 90 provided 34% of naphthoate 91. Protection of the free phenolic function of 82 as a methyl ether (100%) (Me_2SO_4/K_2CO_3), followed by bromination at the benzylic position with N-bromosuccinimide furnished 92b. Displacement of the introduced bromine at the benzylic position of 92b with hydroxide

resulted in anchimerically assisted hydrolysis of the ester function to yield β-sorigenin methyl ether 93b in 85%.

Preparation of α-sorigenin methyl ether 93c was more circuitous. The bromination of naphthalene 91 with an equivalent of N-bromosuccinimide resulted in nearly exclusive formation of ring-brominated product. Successful bromination at the benzylic position of the ring-brominated product was performed with a second equivalent of N-bromosuccinimide and gave the dibromo compound 92a. Transformation of 92a to the naphthalide 93a was accomplished by the same procedure described for 93b. Catalytic hydrogenation of the ring-brominated lactone 93a provided α-sorigenin methyl ether 93c in 54% overall yield from 91.

Our newly developed synthetic methodology described earlier provides a significantly improved ring annelation sequence. Each annelation sequence is accomplished in ca 40% yield. However, this methodology has some limitations; the reaction sequence is lengthy and requires numerous purifications. Furthermore, the Reformatsky reaction is performed at high dilution and requires a large volume of solvent. Although the time required for the Reformatsky reaction is variable and depends upon the amount of starting material used, it usually takes several days to complete a 1~2 gram scale reaction. One serious drawback in the Reformatsky reaction is the in situ demethylation of the starting material by $ZnBr_2$ generated in the reaction. This demethylation is observed to a large extent with 6,8-dimethoxybenzo[2,3-*b*]pyran (90) although it is less significant with monomethoxy compound 81. Furthermore, the ring annelation via the Reformatsky reaction is limited to introduction of only a carboxyl functionality at C-2. Although there

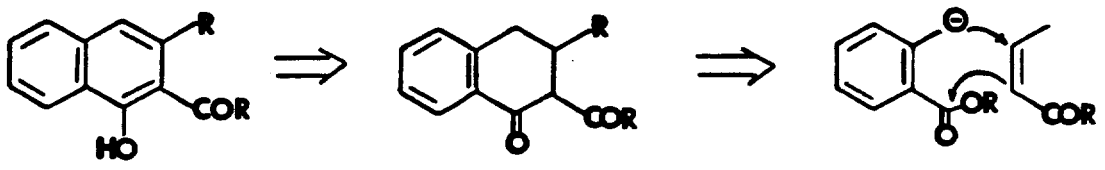
exists the potential for manipulation of this 2-carboxyl functionality to other functional groups, it would be desirable for natural products syntheses to directly introduce a wide variety of electron withdrawing substituents at this position.

IV. NEW AROMATIC RING ANNELATION METHODOLOGY

The validity of the strategy of repetitive ring annelation as a route to polynuclear aromatic systems has been demonstrated.[26,32] The ring annelation sequence provides a significantly abbreviated methodology for the efficient regiospecific preparation of diverse linear polynuclear aromatic systems of natural origin.

While each annelation sequence is accomplished in some 40% yield, numerous steps are required as are numerous purifications. Particularly time consuming is the high dilution Reformatsky reaction. A further problem is that, while the C-2 carboxyl group is a manipulable functionality, it would be desirable to have methodology which would permit direct introduction of a wider diversity of electron withdrawing substituents at C-2. For these reasons a study was undertaken to find a more efficient methodology for ring annelation which would also permit direct introduction of a larger variety of electron withdrawing substituents at C-2.

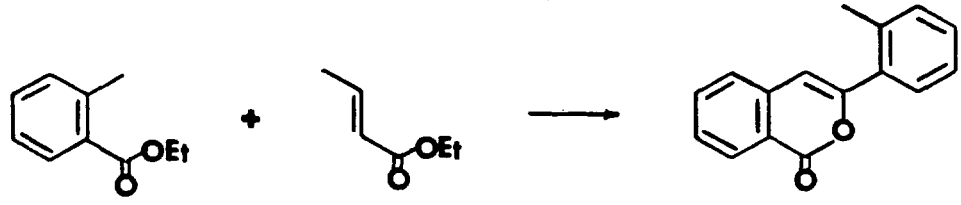
One antithetic analysis of an aromatic ring rendered the



plausible route shown above. Conjugate condensation of an ortho-toluate with a Michael acceptor would lead to ring closure yielding a tetralone. In subsequent steps, the tetralone ring would be aromatized.

The concept was tested by condensing the anion of ethyl ortho-toluate (1), generated at -78°C with lithium diisopropylamide (LDA), with ethyl trans-2-butenoate (2). The reaction failed to give the tetralone; instead, the dimerization product 3 was produced (Scheme IV-1)

Scheme IV-1

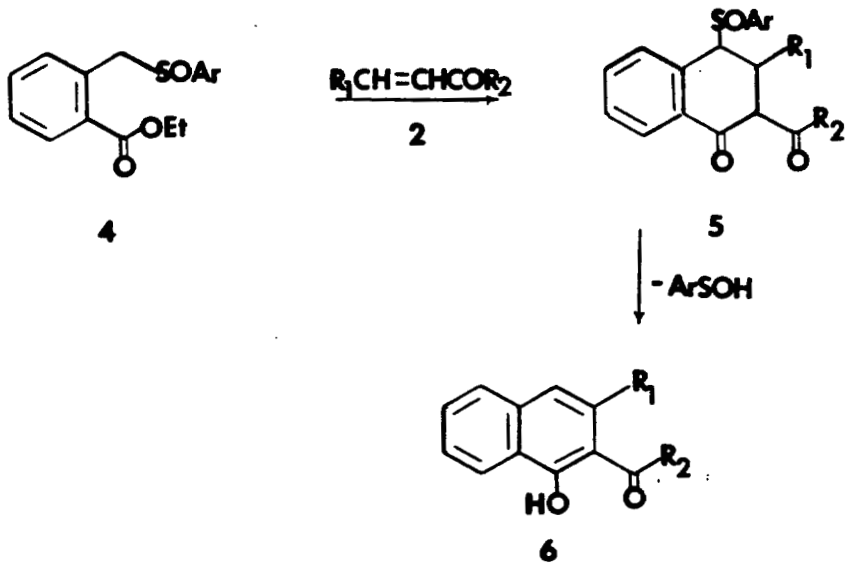


1 2 3

Nevertheless, the failure of the reaction provided a key piece of information. To insure the success of the reaction, an electron withdrawing functionality capable of stabilizing a carbanion on the benzylic position would be needed.

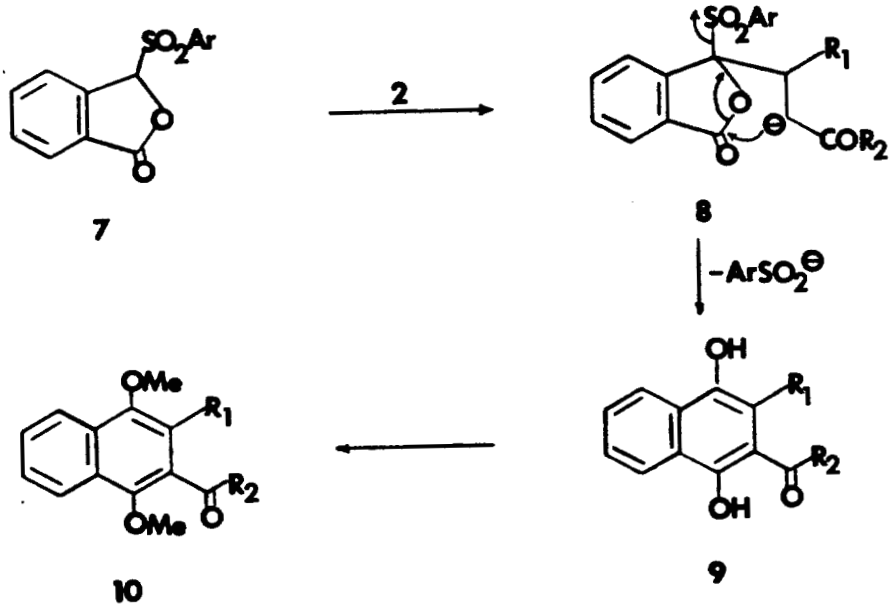
The phenylsulfoxide group was selected for use since it would provide not only the needed carbanion stabilization, but also there existed the possibility that it could be directly extruded to aromatize the tetralone ring (Scheme IV-2).

Scheme IV-2



Further modification of this approach using 3-phenylsulfonyl-1(3H)-isobenzofuranone (7) would provide a direct route to 1,4-dihydroxy-napthalenes (9) (Scheme IV-3). In this route, the sulfone functionality

Scheme IV-3



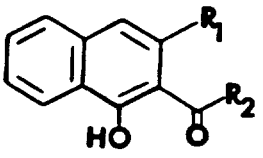
serves a dual purpose. It provides initial carbanion stablization, then later serves as a leaving group. Tautomerization of the diketone intermediate then yields dihydroxy naphthalene 9.

A. Sulfoxide Route

The ethyl 2-phenylsulfinylmethylbenzoate(4) was prepared from ortho-toluate (1) by bromination with N-bromosuccinimide at the benzylic position, followed by displacement of the introduced bromine with sodium thiophenoxide. Oxidation of the sulfide to the sulfoxide was accomplished using either sodium periodate in methanol-water at room temperature,[33] or better with m-chloroperbenzoic acid in methylene chloride at -78°C.[34]

The anion of 4 was generated at -78°C using lithium diisopropylamide and the resulting orange-brown anion was allowed to react with various Michael acceptors. Thin layer chromatographic analysis of the reaction mixture immediately after warming to room temperature showed the presence of a small amount of naphthol 6 along with another product, which slowly disappeared at room temperature with concomitant formation of the desired naphthol. It was presumed that the new product could be either the intermediate tetralone 5 or the initially formed Michael adduct. The reaction was normally taken to completion by heating at reflux until there was no further change in tlc analysis. In Table I, various 1-hydroxynaphthalene products prepared by this procedure are listed.

TABLE I: 1-Hydroxy-2,3-disubstituted Naphthalenes (6) Prepared by Reactions of 2-Phenylsulfinylmethylbenzoate (4)with various Michael Acceptors.

Compound 6		R_1	R_2	% Yield	mp, °C
	a	H	OEt	28	48-49 (lit.[35] 49)
	b	H	CH_3	37	100-101 (lit.[36] 101)
	c	CH_3	OEt	57	58-59 (lit.[30] 56-59)
	d	CH_3	CH_3	70	93-93.5
	e	CH_2SCH_3	OEt	64	59-60
	f	$(CH_2)_3$			

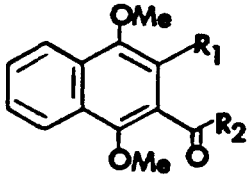
B. Sulfone Route

Preparation of 3-phenylsulfonyl-1(3H)-isobenzofuranone (7) was accomplished using phthalaldehydic acid as starting material. Refluxing phthaladehydic acid with benzenthiol in benzene with a catalytic amount of p-toluenesulfonic acid with continuous removal of water gave 3-phenylthio-1(3H)-isobenzofuranone in 95% yield.[37] The phenylthio compound was oxidized to 3-phenylsulfonyl-1(3H)-isobenzofuranone (7) with m-chloroperbenzoic acid.[38]

The yellow anion of sulfone 7 was generated in tetrahydrofuran at -78°C with lithium diisopropylamide and allowed to react with various Michael acceptors. The reaction mixture was brought to room temperature and stirring was continued for 2 hours. Thin layer chromatographic analysis at this point indicated that the intermediate was almost completely converted to the desired 1,4-dihydroxynaphthalene. It was observed that the dihydroxynaphthalenes 9 formed in this reaction

rapidly underwent air oxidation to naphthoquinones. Hence, the final products were isolated as the dimethyl ethers 10 by methylating the phenolic functionalities with dimethyl sulfate and anhydrous potassium carbonate in refluxing acetone. The dimethoxynaphthalenes prepared by this method are presented in Table II.

TABLE II: 1,4-Dimethoxynaphthalenes (10) Prepared by Reaction of 3-Phenylsulfonyl-1(3H)-isobenzofuranone (7) with various Michael Acceptors.

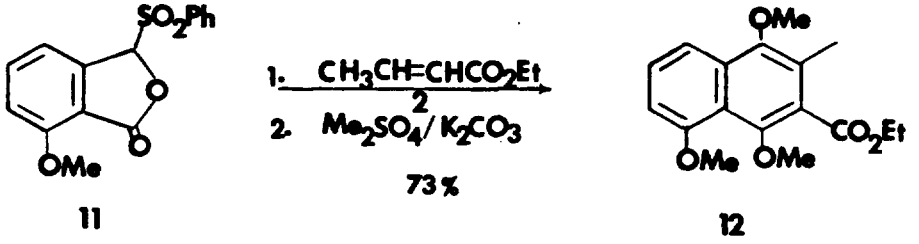
Compound 10		R_1	R_2	% Yield	mp, °C
	a	H	OEt	32	a
	b	H	CH_3	29	59-60
	c	CH_3	OEt	70	a
	d	CH_3	CH_3	86	70-72
	e	CH_2SCH_3	OEt	28	a
	f	$(CH_2)_3$		69	119-120

a=oil

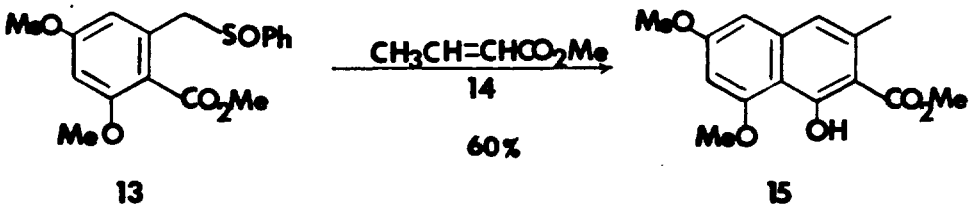
The yields of naphthalene products were generally enhanced when there was an alkyl substituent on the β-carbon of the Michael acceptor. The low yields of products from 3-butene-2-one and ethyl propenoate are undoubtedly due to the polymerization of these reagents under the basic reaction conditions. It was assumed that the increased yields of products obtained from the sulfone as compared with those from the sulfoxide were due to the enhanced stablization of the carbanion by the presence of sulfonyl functionality.[39] This conclusion

is further supported by the observation that the sulfone 7 reacted quite smoothly with the notoriously poor Michael acceptor 2-cyclohexene-1-one while the sulfoxide 4 did not react and failed to furnish any product.[40]

The scope and potential applicability of this new ring annelation methodology to natural product synthesis were demonstrated by the



11 12 Eq.1



13 15 Eq.2

preparation of more highly functionalized naphthalene systems such as ethyl 3-methyl-1,4,8-trimethoxy-2-naphthoate (12) from 7-methoxy-3-phenylsulfonyl-1(3H)-isobenzofuranone (11) and ethyl trans-2-butenoate (2) (Eq. 1), and methyl 6,8-dimethoxy-1-hydroxy-3-methyl-2-naphthoate (15) from methyl 4,6-dimethoxy-2-phenylsulfinylmethylbenzoate (13) and methyl trans-2-butenoate (14)(Eq.2). The yields of these products were virtually identical with those obtained with the unsubstituted compounds.

The newly developed ring annelation methods for the preparation

of 1-hydroxynaphthalenes and 1,4-dihydroxynaphthalenes represent powerful adjunct methodology to the repetitive ring annelation strategy for construction of linear polynuclear aromatic systems of natural origin.[41] To demonstrate the efficacy of this adjunct methodology, synthesis of a natural product using these reactions was undertaken.

V. SYNTHESIS OF METHYL KIDAMYCINONE

A. Background

Kidamycin (16a),[7] hedamycin (17),[8] indomycin,[9] pluramycin A,[10] and neopluramycin[10a] are members of a large family of antibiotics produced by Streptomyces species. These antibiotics have, as a common structural feature, a functionalized 4H-anthra[1,2-*b*]pyran nucleus (Fig. 1). Due to the complexity of these antibiotics, only the structure of kidamycin had been fully determined and that required extensive chemical and spectral studies as well as x-ray analysis.[7] The structure of hedamycin was proposed as 17 on the basis of a spectral comparison of hedamycin and kidamycin.[8]

From the following structure, it can be seen that kidamycin has, as a unique skeletal feature, two different C-aminosugar residues attached to the D-ring of the anthra[1,2-*b*]pyran skeleton.

Kidamycin is known to exhibit significant cancerostatic activity against several animal tumors such as Erlich ascites tumor, Sarcoma 180 solid tumor, Friend Virus induced leukemia, and AH-66F ascites Heptoma.[7,42] It is believed that the mechanism by which this antibiotic exhibits its activity is through inhibition of nucleic acid synthesis. No chemical synthesis of the aglycone portion kidamycinone (16b) or of the antibiotic has been reported.

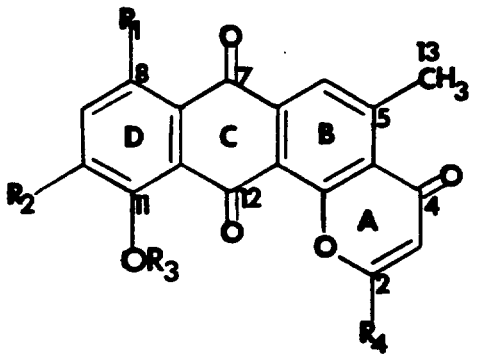


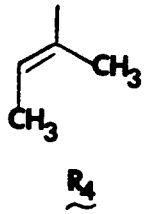
Fig. 1

16a Kidamycin

R_1 = Angolosamine

R_2 = N,N-dimethylvancosamine

R_3 = H



16b Kidamycinone

$R_1 = R_2 = R_3 = H$

16c Methyl kidamycinone

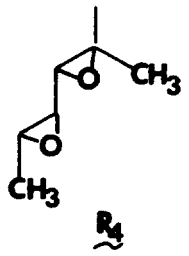
$R_1 = R_2 = H$, R_3 = Me

17 Hedamycin

R_1 = angolosamine

R_2 = N,N-dimethylvancosamine

R_3 = H



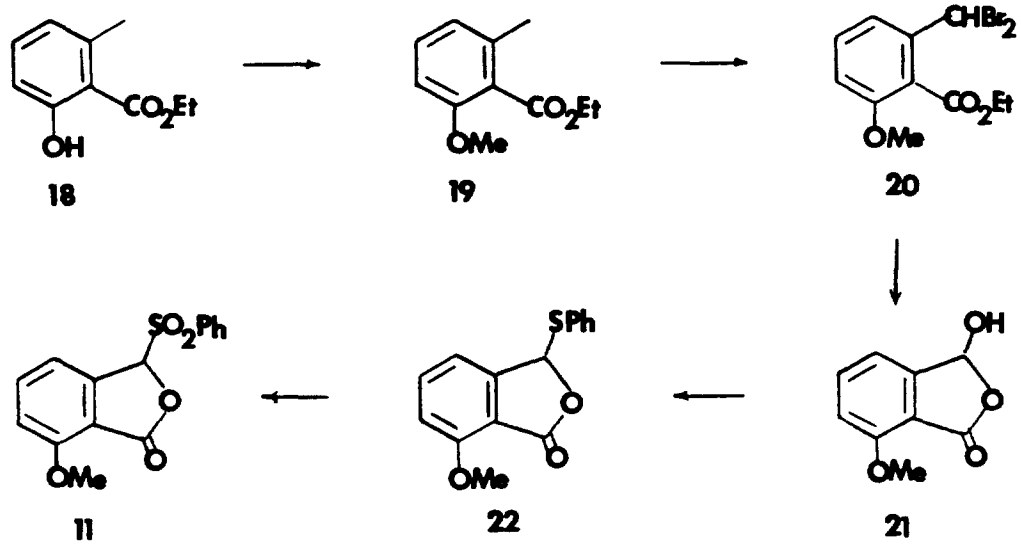
B. Synthetic Plan

The synthetic plan leading to the antibiotic aglycone methyl kidamycinone (16c) was initially to construct regioselectively, using the strategy and new ring annelation methodology, the key intermediate anthracene 27. The ortho-disposed phenolic group and acetyl functionality of 27 would then be employed to fashion the pyrone moiety.

1. Preparation of the Anthracene Portion (27)

In order to prepare the anthracene portion of methyl kidamycinone (16c), the starting material 7-methoxy-3-phenylsulfonyl-1(3H)-isobenzofuranone (11) was prepared from ethyl 2-hydroxy-6-methylbenzoate (18)[43] by the five-step reaction sequence shown in Scheme V-1.

Scheme V-1

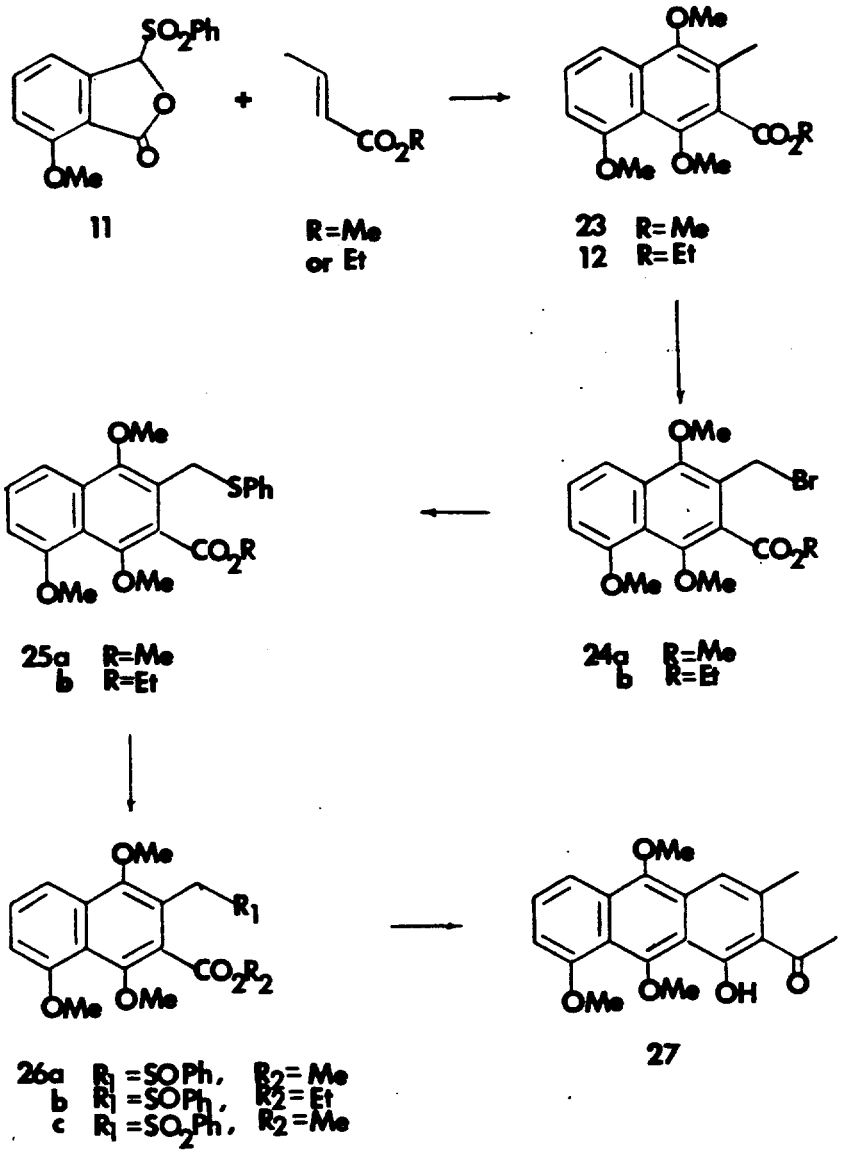


Methylation of phenol 18 with dimethyl sulfate and anhydrous potassium carbonate gave methyl ether 19 (100%). Selective bromination of the

methyl group of 19 with 2 equivalents of N-bromosuccinimide afforded dibromo compound 20, which was hydrolyzed in aqueous hydrochloric acid and acetic acid[44] to give 3-hydroxy-7-methoxy-1(3H)-isobenzofuranone(21) in 80% yield. Replacement of the hydroxyl group in 21 with a thiophenyl residue was accomplished by heating a mixture of 21 and benzenethiol in benzene under reflux with a catalytic amount of p-toluenesulfonic acid to furnish sulfide 22 (72%).[37] Oxidation of sulfide 22 to sulfone 11 was performed in 96% yield with 2 equivalents of m-chloroperbenzoic acid.[38]

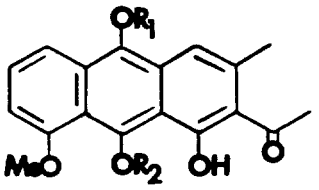
Using sulfone 11 obtained above, the key intermediate, anthracene 27, was prepared (Scheme V-2). Condensation of the anion of sulfone 11 (lithium diisopropylamide, -78°C) with methyl trans-2-butenoate (14) yielded an intermediate 1,4-dihydroxynaphthalene, which was methylated immediately with dimethyl sulfate and anhydrous potassium carbonate to give regiospecifically constructed naphthalene 23 in 83% yield. Benzylic bromination of naphthoate 23 with N-bromosuccinimide afforded bromomethyl naphthoate 24a which was converted to sulfide 25a by heating with sodium thiophenoxide in ethanol under reflux. The overall yield of 25a from 23 was 89%. Oxidation of sulfide 25a to sulfoxide 26a was accomplished either with sodium metaperiodate[33] or with m-chloroperbenzoic acid.[34] Although the reaction required a prolonged period of time for completion, oxidation of 25a with sodium metaperiodate provided 26a as the sole product (95%). On the other hand, the oxidation of 25a with m-chloroperbenzoic acid was completed in 30 minutes. The product (88%) obtained by this latter method was accompanied by a small amount (9%) of sulfone 26c, which was readily separated.

Scheme V-2

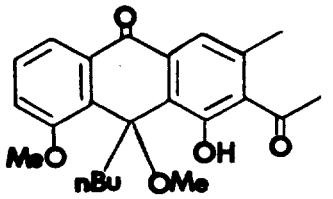

SO2Ph
OMe
11
CO2R
R=Me
or Et
23 R=Me
12 R=Et
Br
24a R=Me
b R=Et
SPh
25a R=Me
b R=Et
R1
CO2R2
26a R1=SOPh, R2=Me
b R1=SOPh, R2=Et
c R1=SO2Ph, R2=Me
OH
27

Condensation of the anion of sulfoxide 26a (lithium diisopropylamide, -78°C) with 3-pentene-2-one furnished, following thermal elimination of phenylsulfenic acid (PhSOH), regiospecifically constructed, selectively protected anthracene 27 in 71% yield as a fluorescent, orange-colored solid. Anthracene 27 was unstable and underwent air oxidation to quinone 30 on standing at room temperature.

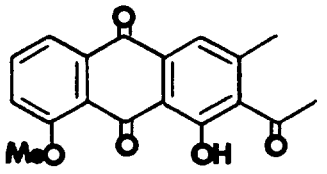
When the methyl ester function of sulfoxide 26a was replaced with an ethyl ester, condensation with 3-pentene-2-one yielded a substantial amount of ethoxy substituted anthracene 28a (23%) as well as the desired compound 27 (39%). Although structure 28b could not be excluded for the ethoxy substituted anthracene 28a, tangible evidence for the structure 28a was obtained by comparison of the ^{1}H NMR



28a R_1= Et R_2=Me
b R_1= Me R_2= Et



29



30

spectra of the compound obtained in carbon tetrachloride and in benzene. It is known that the solvent effect of benzene on the chemical shifts of unhindered methyl protons are significantly larger when compared with highly hindered methyl protons.[45] A similar observation

was made in the case of the ethoxy substituted anthracene 28a. The six protons corresponding to the two methoxy functions at C-8 and C-9 appear as a singlet at δ 3.96 in carbon tetrachloride. In benzene solution they are moved to higher field and appear as singlets at δ 3.75 and 3.46, respectively. It is believed that the larger increment, corresponding to the peak at δ 3.46 in benzene is due to the unhindered methoxyl protons at C-8 and the small increment corresponding to the singlet at δ 3.75 in benzene is from the highly hindered methoxyl protons at C-9. Further evidence for the solvent effect was obtained with trimethoxy anthracene 27. In carbon tetrachloride, the three methoxyls at C-8, 9, 10 in 27 were observed as two singlets at δ 3.99 (6H) and 3.96 (3H). In benzene solution however, the two unhindered methoxyls at C-8 and C-10 shift upfield to a large extent and appear as a singlet at δ 3.46, whereas the hindered methoxyl at C-9 shifts to a lesser extent and appears as a singlet as δ 3.75. Anthracene 28a was extremely unstable and underwent decomposition to give anthraquinone 30 at room temperature.

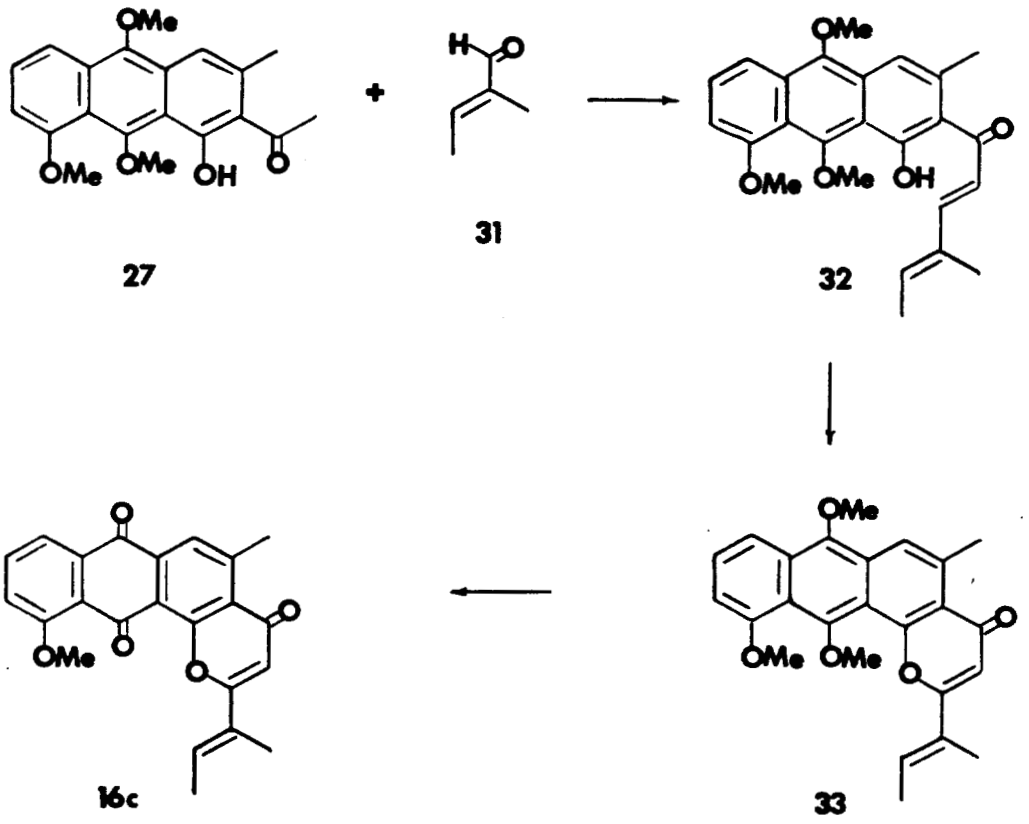
When the condensation of the anion of sulfoxide 26a with 3-pentene-2-one was performed with a slight excess of n-butyllithium, the reaction gave, in addition to compound 27, a small amount of an extremely unstable compound, which was assigned structure 29 on the basis of its ^{1}H NMR and mass spectra. Anthrone 29 was unstable even at low temperatures, rapidly decomposing to an unidentifiable mixture of products.

2. Construction of the Pyrone Ring

Having efficiently prepared key intermediate anthracene 27, construction of the pyrone portion using the ortho-hydroxyl and acetyl functionalities present in anthracene 27 was undertaken. Various approaches and reaction sequences investigated were unsuccessful. Aldol condensation of 27 with tiglaldehyde (31) using a conventional reagent like ethanolic potassium hydroxide[46] failed to furnish dienone 32. Instead, decomposition of the starting aldehyde was noted.

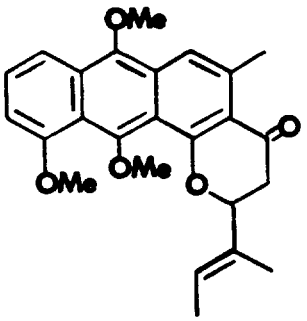
After a lengthy investigation, a sequence to convert anthracene 27 to trimethoxyanthrapyran 33 was found. Oxidative demethylation of 33 at C-7 and C-12 then furnished methyl kidamycinone (16c) (Scheme V-3). Transformation of anthracene 27 to ortho-hydroxy-

Scheme V-3

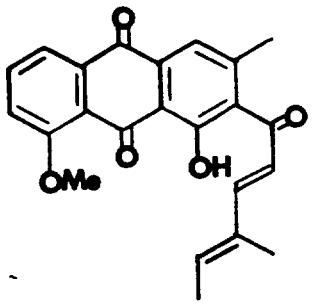


dienone 32 was accomplished in 75% yield by converting 27 to a dilithium anion using lithium diisopropylamide in tetrahydrofuran at -78°C, which was then reacted with tiglaldehyde (31).

The large coupling constant (J = 15 Hz) of the newly formed olefinic protons appearing at δ 6.98 and 6.40 permitted assignment of the configuration as trans. Dehydrocyclization of ortho-hydroxydienone 32 to trimethoxyanthrapyrone 33 was accomplished in 27% yield by heating 32 with selenium dioxide in *t*-amyl alcohol. It is well known that selenium dioxide which becomes selenious acid in water or an alkoxy selenate in alcohol, catalyzes cyclization reactions of ortho-hydroxyenone systems and at the same time promotes oxidation reactions to give benzo-4-pyrones. Although the mechanism of the reaction is not clearly understood, this method has been employed to convert a variety of chalcones to flavones.[46a,47] The dehydrocyclization reaction of 32 with selenium dioxide yielded, in addition to the desired anthrapyrone 33, dihydroanthrapyrone 34 (10%), anthraquinone 35 (13%), and unreacted starting material 32 (50%). The unreacted material was re-



34



35

covered and transformed to the desired compound, which brought the total yield of 33 up to 33% from 32. Several attempts were made to

optimize the conditions for the conversion of 32 to 33. Various solvent systems such as *n*-amyl alcohol, *i*-amyl alcohol, and ethanol were tried. However, none of these solvents seemed to be appropriate for the reaction since they either gave lower yields of the desired product or destroyed the starting material.

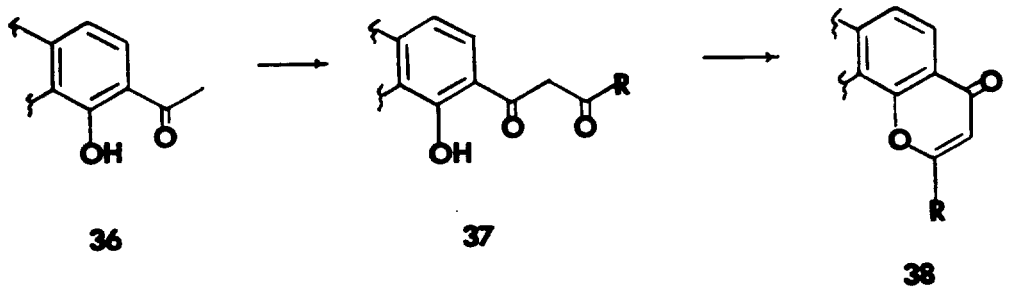
Having trimethoxyanthrapyrone 33 in hand, the remaining step in the synthesis was to deprotect the methoxy functions at C-7 and C-12. Oxidative demethylation of compound 33 with silver oxide[48] in the presence of dilute nitric acid furnished monomethoxyanthrapyrone 16c in 83% yield, thus completing the first total synthesis of methyl kidamycinone (16c).

C. Other Approaches Directed toward the Construction of Pyrone Ring

1. ortho-Hydroxy-1,3-diketone Route

There are numerous reports of syntheses of benzo-4-pyrone systems from ortho-hydroxyacetophenone analogs. A commonly employed method is to convert the ortho-hydroxyacetophenone analog 36 to an ortho-hydroxy-1,3-diketone 37, then cyclize and dehydrate the resulting

Scheme V-4



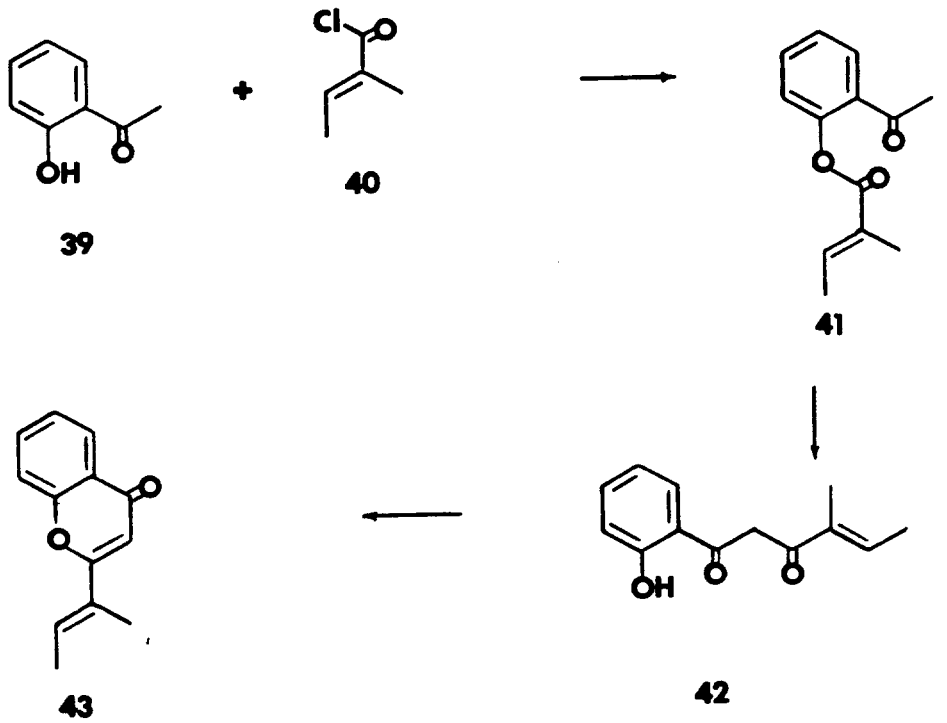
36 37 38

1,3-diketone using an acid catalyst to give the benzo-4-pyrone 38 (Scheme V-4).

Although preparation of ortho-hydroxy-1,3-diketone 37 from 36 could be achieved by various methods, two appraoches have been investigated in the current study. One approach was the use of an internal Claisen condensation, the Baker-Venkataraman method[49,50] and the other was a direct acylation procedure.

Prior to carrying out the construction of the ortho-hydroxy-1,3-diketone intermediate with anthracene 27, a model sequence using ortho-hydroxyacetophenone (39) was investigated (Scheme V-5). Condensation of 39 with tigloyl chloride (40) in pyridine gave ester 41.[51] Transfer of the tigloyl group to give 1,3-diketone 42 was performed by heating ester 41 with excess sodium hydride in dioxane.[52] The ortho-hydroxy-

Scheme V-5

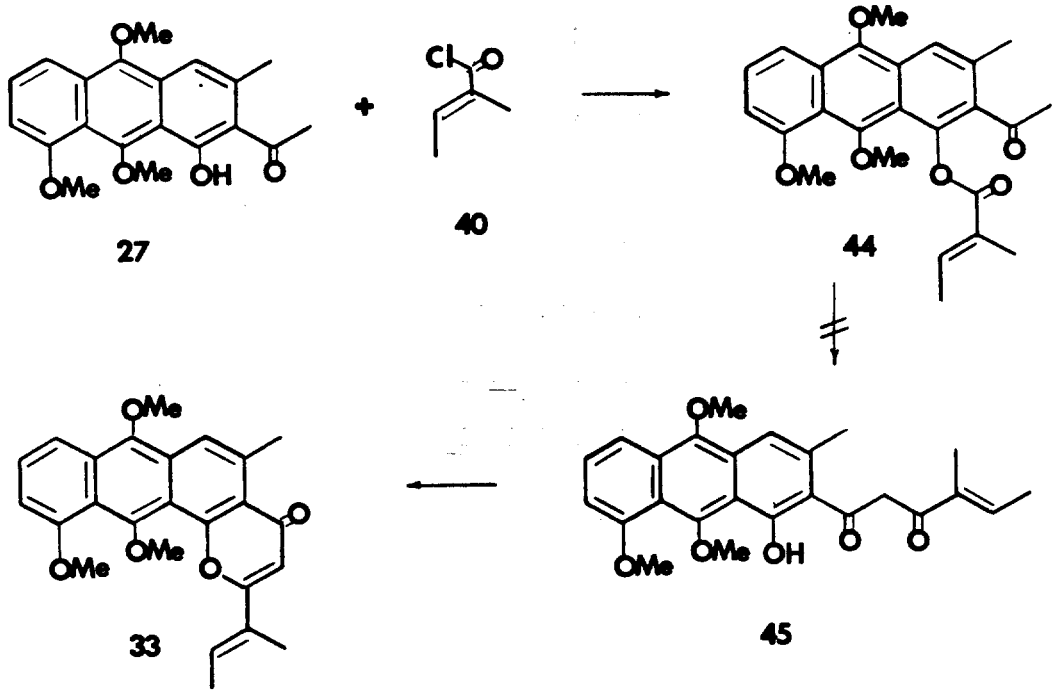


1,3-diketone 42 was cyclized and dehydrated to benzo-4-pyrone 42 on treatment with glacial acetic acid in the presence of sodium acetate.[52] The overall yield of 43 from 39 was 75%.

(a) Baker-Venkataraman Route using Anthracene Ester 44

Having successfully demonstrated the model pyrone preparation, the parallel synthetic procedure depicted in Scheme V-5 was undertaken to transform anthracene 27 to the desired anthrapyran 33 (Scheme V-6). Heating a mixture of anthracene 27 and tigloyl

Scheme V-6

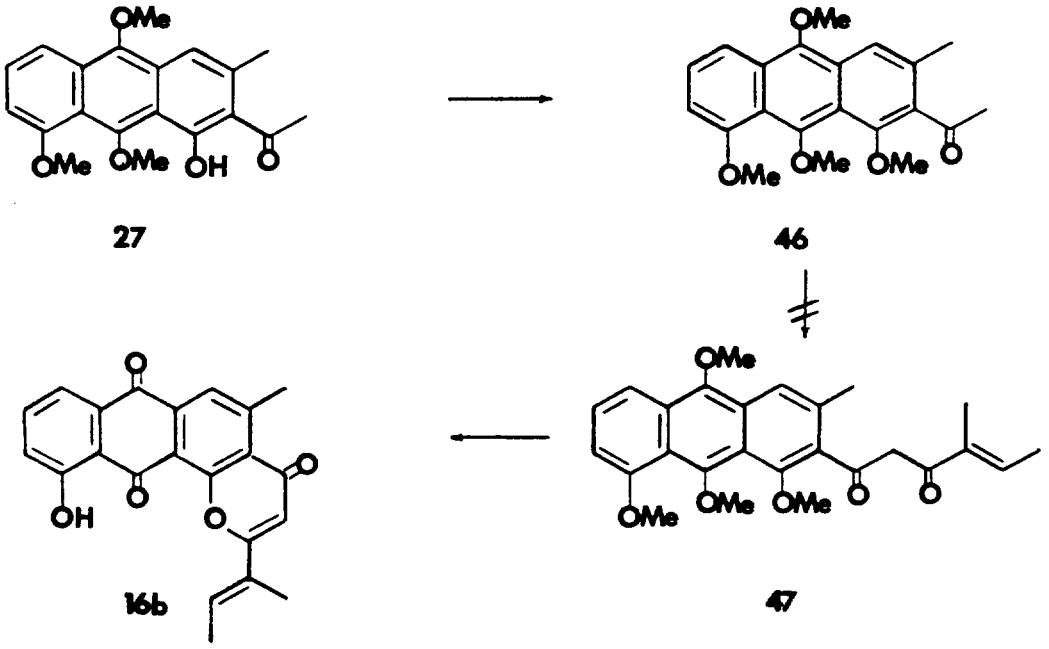


chloride (40)[52,53] in pyridine gave the expected ester 44 in 80% yield. Attempted transfer of the tigloyl group to the acetyl functionality with sodium hydride[52] in dioxane was unsuccessful as was the use of alternative reagents such as potassium hydroxide in pyridine[53] and boron trifluoride etherate ($BF_3.OEt_2$).

(b) Direct Acylation Route

Since the conversion of 44 to 1,3-diketone 45 via the Baker-Venkataraman method was not feasible, an approach was devised to directly introduce the tigloyl function at the carbon α to the ketone of 27. Attempted condensation of 27 with methyl tigloate[54] employing sodium hydride[55] failed. It was felt that masking of the phenolic functionality with a protective group which could be readily removed just before cyclization was needed. The trimethylsilyl ether of the phenol seemed best suited for this specific need. However, attempts to silylate the phenolic group of 27 with chlorotrimethylsilane in triethylamine[56] or hexamethyldisilazane[57] in the presence of chlorotrimethylsilane did not produce an isolable product.

Scheme V-7



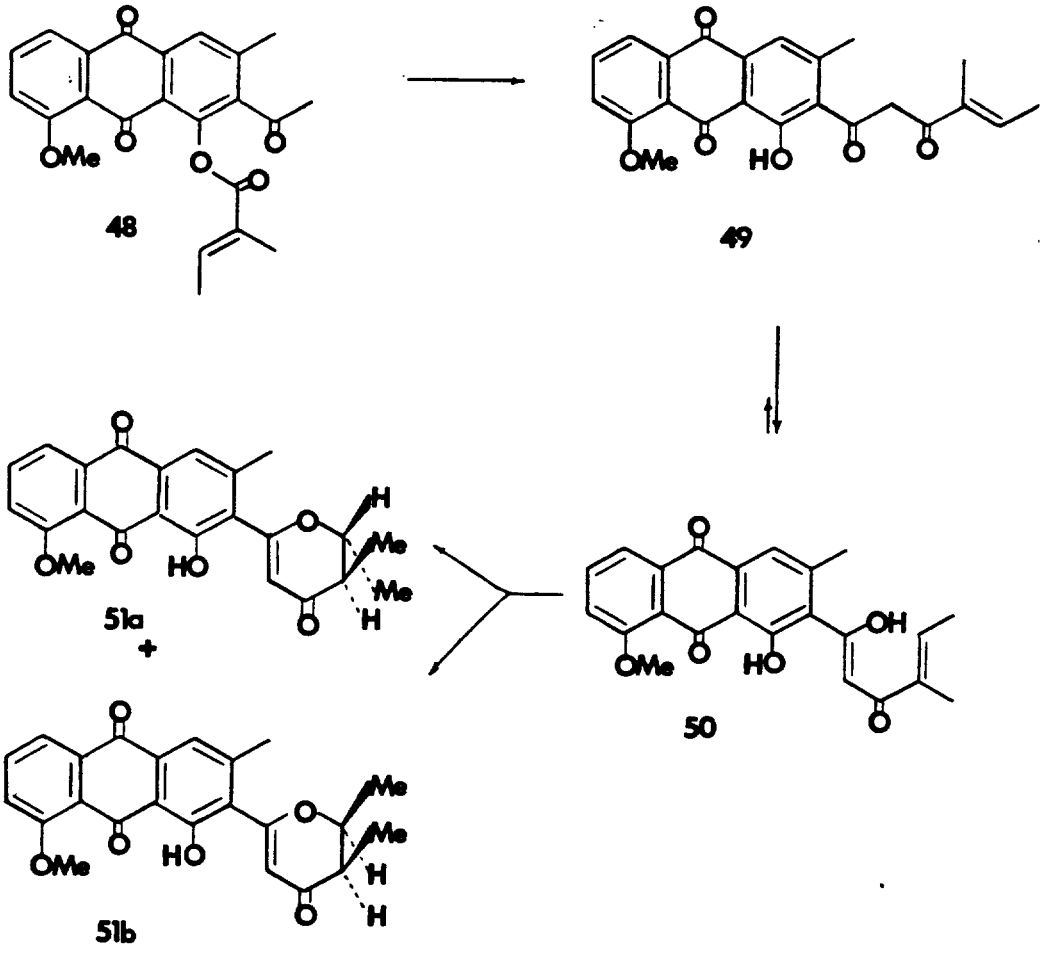
It was then decided to mask the free phenolic functionality of 27 with a methyl group and convert the resulting permethylated

anthracene 46 to 1,3-diketone 47 by direct acylation of the acetyl group (Scheme V-7). Demethylation of the tetramethoxy-1,3-diketone 47 followed by cyclization, would then lead to the formation of kidamycinone (16b). Methylation of 27 with dimethyl sulfate and potassium carbonate in acetone provided the permethylated anthracene ether 46 in 91% yield. Attempts to condense the methyl ketone of 46 with tigloyl chloride (40) or methyl tigloate were carried out employing bases[58] such as potassium *t*-butoxide, sodium hydride, and lithium diisopropylamide (LDA). However, none of these reactions provided the desired 1,3-diketone 47.

(c) Baker-Venkataraman Route using Anthraquine Ester 48

In earlier experiments (Scheme V-6), it was observed that the attempted acyl transfer reaction of anthracene ester 44 to 1,3-diketone 45 was not successful. It was speculated that the ease of decomposition of the starting material was due to the lability of the 9,10-dimethoxy functionalities of 44. Therefore, it seemed reasonable that base-catalyzed internal Claisen condensation of the tigloyl ester of anthraquinone 48, devoid of these labile methoxy functions, would give 1,3-diketone 49. As was anticipated, the isomerization reaction of anthraquinone ester 48 with sodium hydride in dioxane produced 49 in excellent yield (Scheme V-8). Since the resulting 1,3-diketone 49 was rather unstable, the product was, without further purification, immediately submitted to cyclization. The presence of an olefinic proton at δ 6.0[59] in the ^{1}H NMR spectrum of 49 indicated that the compound existed mostly in the more stable enol form 50. Heating 1,3-diketone 49 (or 50) in glacial acetic acid in the presence of sodium

Scheme V-8



acetate[52] led to consumption of 49 and production of two new compounds, which were isolated and separated. Neither of the products was, however, the desired methyl kidamycinone (16c). Instead, the new compounds were alternate cyclization products 51a (76%) and its epimer 51b (22%).

That these new products were the compounds 51a and 51b rather than the desired product was readily apparent from their ^{1}H NMR spectra. The ^{1}H NMR spectra of both products 51a and 51b exhibited two doublets at ca δ 1.25 and 1.55, which correspond to the two methyl groups adjacent

to methine protons and a singlet at δ 13.28 in each case for the hydrogen bonded phenolic hydrogen. Perhaps, the most crucial information was the one proton singlet appearing at about δ 5.60 in the spectra of both products, which was assigned as the olefinic proton of the newly formed pyrone ring. The olefinic proton α to the ketone in benzo-4-pyrone systems normally appears at much lower field as a singlet in the region between δ 7.5 and 6.0.[52] In addition, the large coupling constant

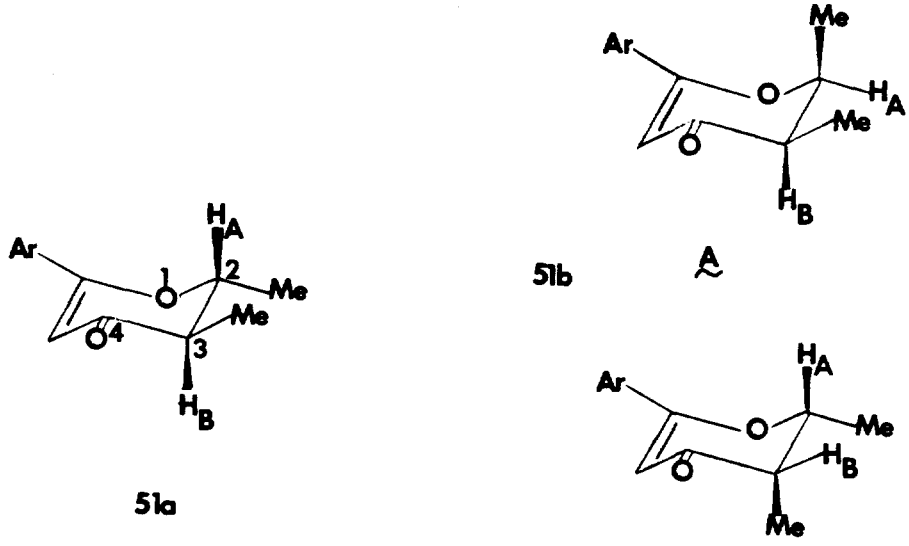


Fig. 2

(J_{AB} = 12 Hz) for AB hydrogens observed at δ 2.53 ($CO\underline{CH}CH_3$) and 4.44 ($O\underline{CH}CH_3$) in the spectrum of 51a indicates that the methine protons at C-2 and C-3 of the pyrone ring are in the diaxial configuration (Fig.2). Although structure B cannot be excluded for the minor product 51b upon considering the smaller coupling constants of the AB hydrogens (J_{AB} = 3.4 Hz), structure A has been assigned for 51b on the basis of the chemical shifts. In the ^1H NMR spectrum of 51b, only the methine

proton at C-2 (δ 4.84) is shifted downfield by about 0.4 ppm, compared to that of 51a. This indicates that the stereochemistry of the methine proton at C-2 of 51b is equatorial whereas the same proton in 51a is axial. This is further supported by the fact that, in a fused six-membered ring system, an equatorial proton is usually deshielded by about 0.1 to 0.7 ppm relative to an axial proton on the same carbon.[60]

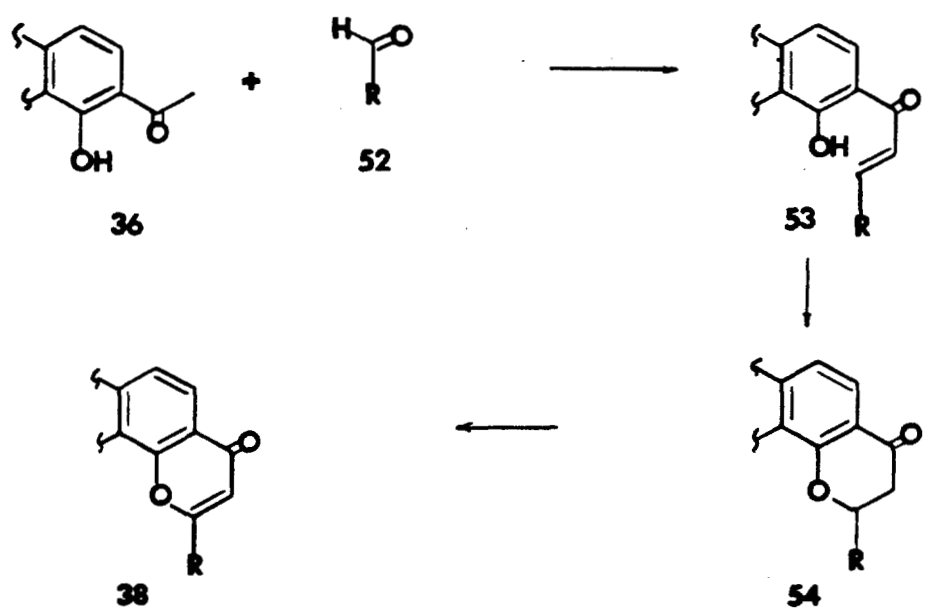
Since construction of the pyrone portion of kidamycinone from 48 via the Baker-Venkataraman procedure was unsuccessful, this method was abandoned.

2. ortho-Hydroxydienone Route

(a) Preparation of ortho-Hydroxydienone

The failure of the previous approach led us to examine an alternative route for the construction of the pyrone skeleton. One method commonly used to build a pyrone fragment is to condense an ortho-hydroxyacetophenone 36 with an aldehyde 52 to

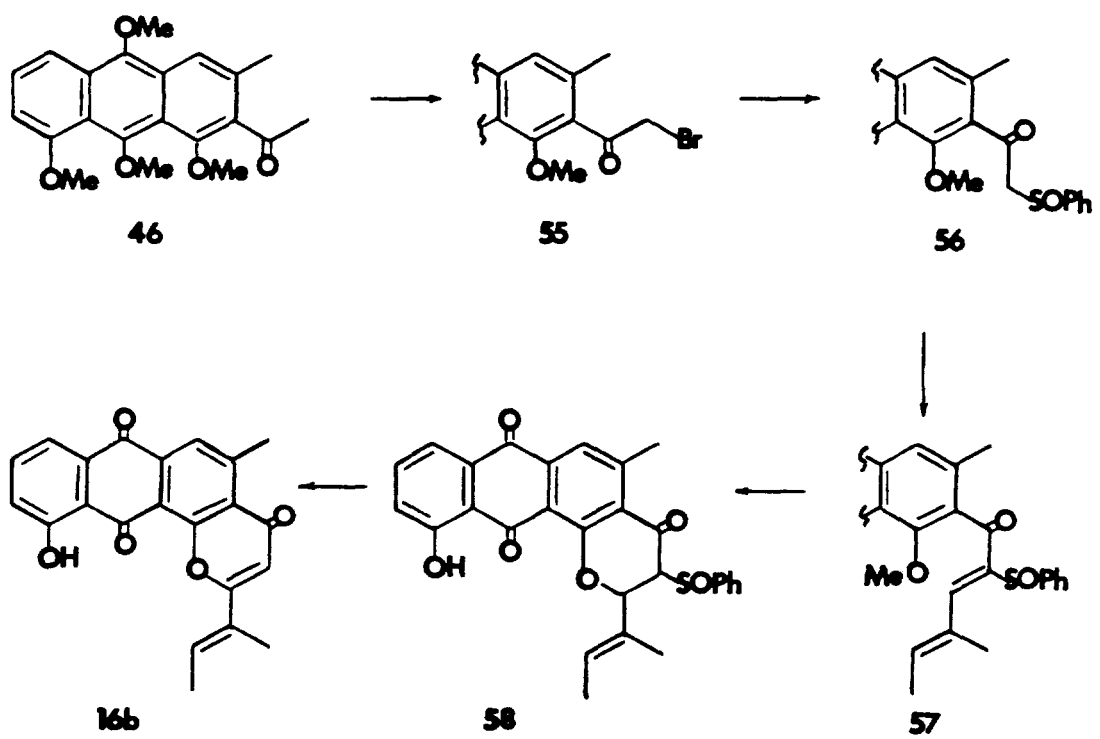
Scheme V-9



give an ortho-hydroxyenone 53. Ring closure of the resulting enone 53 to 54, followed by dehydrogenation of the cyclized product 54 to pyrone 38, then leads to the formation of the pyrone ring (Scheme V-9). This method has been widely employed in the synthesis of flavones and chromenone systems.[61]

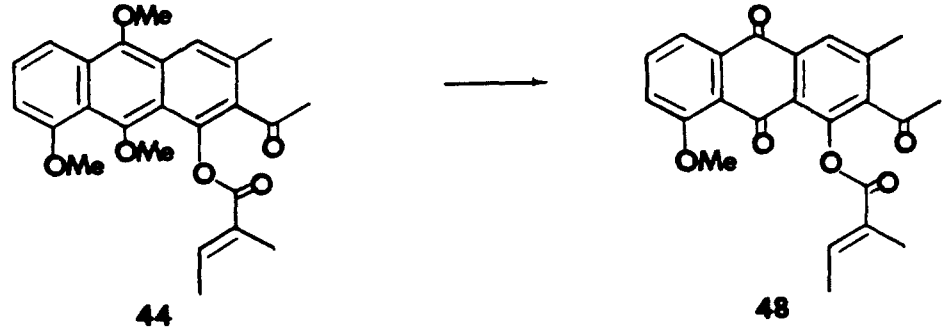
Initially, investigation of the reaction sequence shown in Scheme V-10 was undertaken.[62] A key feature of this approach is that activation of the hindered acetyl function of 46 is accomplished by introducing a phenylsulfinyl group at the carbon α to the ketone. This feature facilitates the aldol condensation of 56 with tigladehyde (31). A further advantage is that the presence of the sulfoxide group

Scheme V-10



in 56 permits facile introduction of a double bond in the cyclized product 58 by a thermal elimination of phenysulfenic acid (PhSOH). Heating the permethylated anthracene 46 with 2 equivalents of cupric bromide in chloroform-ethyl acetate,[63] however, did not produce the desired bromo compound 55. Instead, the reaction produced, via oxidative demethylation by bromide ion, dimethoxyanthraquinone 59 as the major product.

46 59



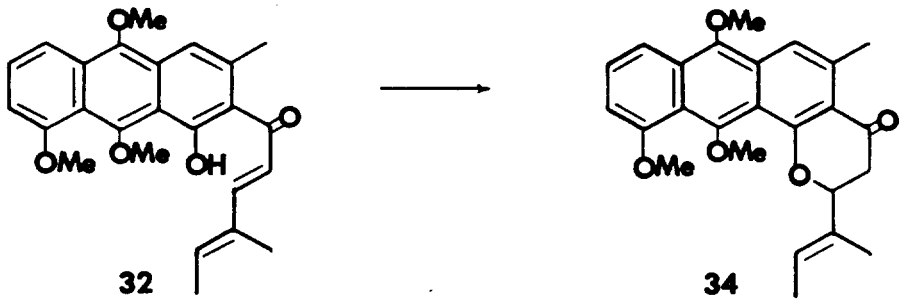
44 48

In the same manner, the tigloyl ester of trimethoxyanthracene 44 gave anthraquinone 48 in 77% yield.

A successful condensation of anthracene 27 with tiglaldehyde (31) using lithium diisopropylamide to give o-hydroxydienone 32 has been previously described in Scheme V-3.

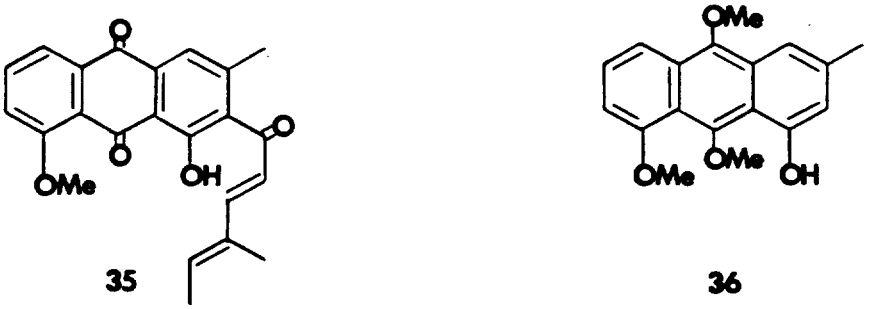
(b) Cyclization of ortho-Hydroxydienones

Using the ortho-hydroxydienone 32, numerous unsuccessful attempts were made to transform it to the cyclized compound 34. Acid catalyzed reactions of 32 using a mixture of hydrochloric acid and acetic acid[55c,61] or boron trifluoride etherate ($BF_3.OEt_2$) did not produce the cyclized compound 34, nor did prolonged



32 34

heating of 32 in benzene in the presence of silica gel.[53c] Reactions with basic catalysts such as sodium hydride, sodium methoxide, and alumina (Woelm) were likewise unsuccessful. Heating 32 in pyridine,[46b,64] resulted in the formation of uncyclized anthraquinone 35. When the



35 36

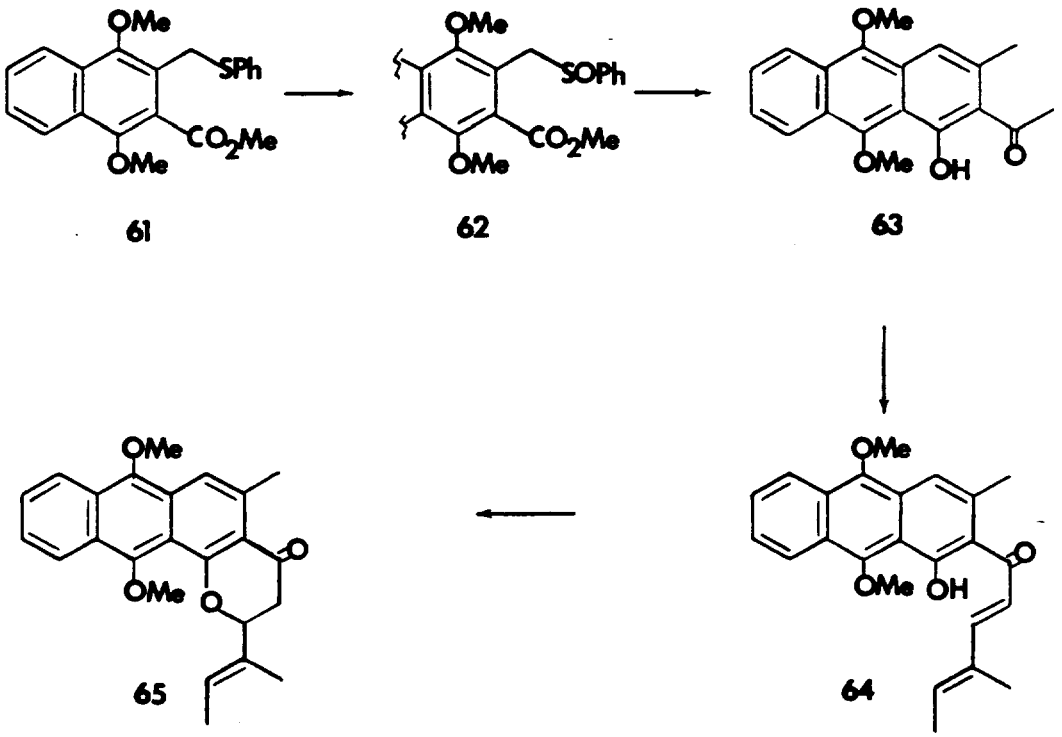
dienone 32 was heated under reflux with sodium methoxide in the presence of a small amount of water anthracene 60, a derivative of the naturally occurring anthraquinone chrysophanol was produced. The formation of 60 presumably involves deacylation by nucleophilic attack of hydroxide ion on the carbonyl functionality of 32.

Reactions with aqueous potassium hydroxide in methanol[65] or sodium acetate in methanol[66] were observed to give the desired cyclized compound 34 along with numerous other side products which could not be identified. Cyclization of 32 to 34 with aqueous potassium hydroxide was rapidly accomplished. However, the reaction was not satisfactory since it led to total consumption of the starting material and produced the desired compound 34 in only 10% yield. Although the reaction was time consuming, the cyclization of 32 conducted with aqueous sodium acetate produced 34 in 35% yield. Moreover, a substantial amount of the unreacted starting material (41%) was recovered and recycled. It seems that, in this cyclization reaction, an equilibrium between the starting o-hydroxyenone and the cyclized product is involved.[61]

(c) Dehydrogenation of 2,3-Dihydroanthrapyran

Having constructed the basic skeleton 34, a method to introduce a double bond in the pyrone ring was sought. Before attempting further reactions with compound 34, model reactions were investigated using 65 prepared from sulfide 61[67] by the route shown in Scheme V-11. The reagents and reaction conditions employed for the synthesis of 65 from 61 were analogous to those described previously for the ring-D methoxylated compound 34.

Scheme V-11

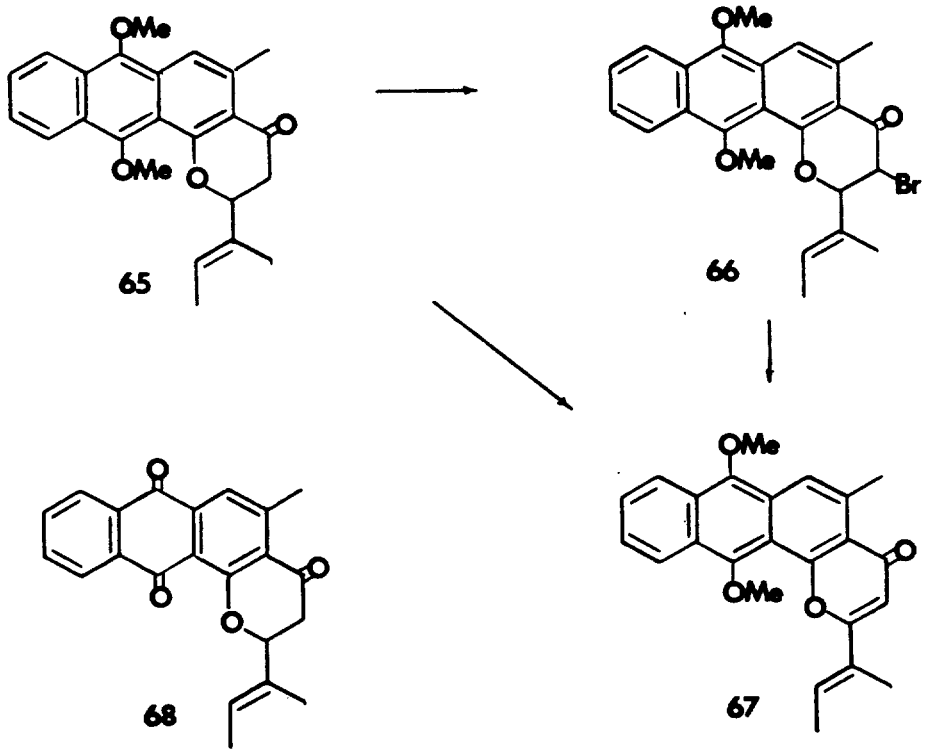


There are a number of methods described in the literature for converting flavanones to flavones and chromanones to chromenones. One of the more common methods is to introduce a functional group such as halogen α to the carbonyl, then dehydrohalogenate the compound.[68] Another method for direct introduction of unsaturation in such systems is by oxidation, using oxidants such as 2,3-dichloro-5,6-dicyanobenzoquinone[53c] or selenium dioxide[53c,69] or iodine in the presence of sodium acetate.[64,70]

Bromination of compound 65 with cupric bromide[68] and with phenyltrimethylammonium perbromide (PTAB)[71] in tetrahydrofuran furnished bromoketone 66 in 39-45% yield, whereas bromination with N-bromosuccinamide gave numerous products,none of which were compound 66

(Scheme V-12). Dehydrobromination of the resulting bromoketone 66

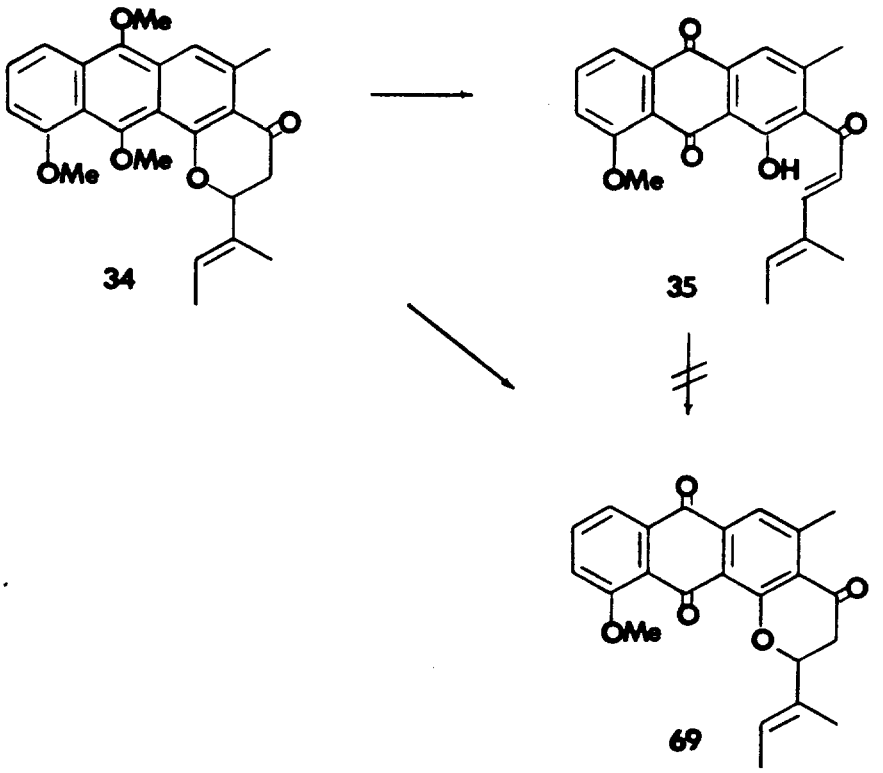
Scheme V-12



with 1,5-diazabicyclo[5.4.0]undec-5-ene(DBU)produced dimethoxyanthrapyran 67[72] as a yellow crystalline compound. Direct oxidation of compound 65 by heating with 2,3-dichloro-5,6-dicyanobenzoquinone in refluxing benzene also provided 67 as well as a small amount of anthraquinone 68.

However, when the methods described above were applied to compound 34 to convert it to anthrapyran 33, none of the desired compound was produced. Instead, the bromination of 34 with cupric bromide in refluxing tetrahydrofuran yielded ring opened compound 35, while

Scheme V-13



the reaction with phenyltrimethylammonium perbromide resulted in the formation of several products, which could not be identified. Oxidation of 34 with 2,3-dichloro-5,6-dicyanobenzoquinone produced anthraquinone 69 (Scheme V-13). Efforts to cyclize ortho-hydroxydienone 35 to 69 using aqueous sodium acetate in methanol or aqueous potassium hydroxide in methanol were unsuccessful. The cyclization failure is probably due to the strong hydrogen bonding between the quinone carbonyl and the adjacent hydroxyl function.

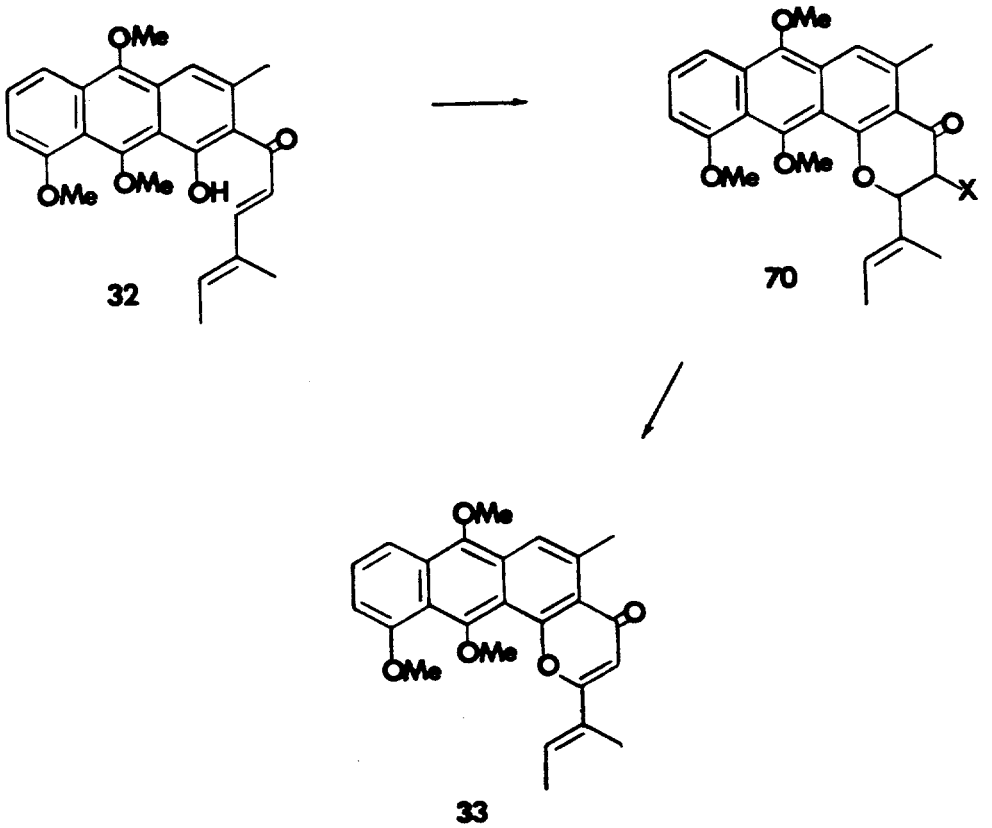
Attempts to prepare anthrapyran 33 from the cyclized compound 34 via direct oxidation using 2,3-dichloro-5,6-dicyanobenzoquinone or selenium dioxide also failed. In both cases a large number of products

were formed with no single compound predominating.

(d) Complexation Route

Since the dihydroanthrapyran 34 failed to provide the anthrapyran 33 either by the bromination-dehydrobromination sequence or by direct oxidation, an alternate procedure was devised to convert ortho-hydroxydienone 32 with an electrophilic reagent (X^+Y^-) in the presence of a base. The electrophile forming the π-complex with the double bond would be incorporated into the cyclized ring by participation of the phenoxide anion yielding compound 70. In subsequent steps HX would be removed introducing unsaturation yielding 33 (Scheme V-14).[50,51] One reagent, appropriate for this scheme is iodine.[73]

Scheme V-14



Other reagents such as benzeneselenenyl chloride (PhSeCl),[74] phenylsulfenyl chloride (PhSCl),[75] bromine,[76] and palladium(II) salts[77] have likewise been utilized in many examples.

Ortho-hydroxy dienone 32 was allowed to react with powdered mixture of iodine and potassium iodide in the presence of pyridine. On stirring the mixture at room temperature, no reaction occurred. Furthermore, when the reaction mixture was heated, the starting material decomposed without giving the desired iodoketone 70. Heating 32 with sodium methoxide or sodium hydride in the presence of palladium acetate did not provide the palladiated compound 70, either. No further attempts to convert 32 to 33 were pursued by using this plan.

SUMMARY

New synthetic methodology for the regioselective annelation of linear polynuclear aromatic systems has been described.

Respective condensation of the anion of ethyl 2-phenylsulfinylmethylbenzoate and 3-phenylsulfonyl-1(3H)-isobenzofuranone with α,β-unsaturated esters and ketones results in regioselective formation of 1-hydroxy-2,3-disubstituted naphthalenes in moderate yield and 1,4-dihydroxy 2,3-disubstituted naphthalenes in good yield.

The efficacy of this synthetic methodology has been demonstrated by an efficient regioselective synthesis of the O-methyl ether of kidamycinone, the methyl ether of the aglycone of the anticancer antibiotic kidamycin.

Condensation of the anion of 7-methoxy-3-phenylsulfonyl-1(3H)-isobenzofuranone(11) with methyl trans-butenoate(14) gave, after methylation, methyl 3-methyl-1,4,8-trimethoxy-2-naphthoate (23). Conversion of the 3-methyl group of 23 to bromomethyl function, followed by displacement of the bromine with thiophenyl residue and oxidation of the resulting phenylthio group furnished methyl 3-phenylsulfinylmethyl-1,4,8-trimethoxy-2-naphthoate(26a). Condensation of the anion of phenylsulfinyl compound 26a with 3-penten-2-one yielded 2-acetyl-1-hydroxy-3-methyl-8,9,10-trimethoxyanthracene(27).

Condensation of 27 with tiglaldehyde gave 2-(4'-methylhexa-2'(E), 4'(E)-dienoyl)-1-hydroxy-3-methyl-8,9,10-trimethoxyanthracene (32). Dehydrocyclization of 32 gave 5-methyl-2(1'-methyl-1'(E)-propenyl)-7,11,

12-trimethoxy-4H-anthra[1,2-*b*]pyran-4-one(33). Oxidative demethylation of 7,12-dimethoxyl groups of 33 furnished O-methyl kidamycinone (16c).

VI. EXPERIMENTAL SECTION

General Comments

Melting points were taken on a Kofler hot-stage microscope and are uncorrected. Infrared spectra were measured with a Perkin-Elmer 621 spectrophotometer and are expressed in cm^{-1}. Ultraviolet spectra were run on a Cary 15 (Varian) ultraviolet-visible spectrophotometer and are expressed in nm. Proton magnetic resonance spectra were obtained with a Varian Model HA-100 using tetramethylsilane (TMS) as the internal standard. Chemical shifts are expressed in δ units. Mass spectra were obtained with CEC DuPont Model 21-110B or DuPont Model 21-491B spectrometers at an ionizing voltage of 70 eV. Carbon-hydrogen analyses were performed by Galbraith Laboratories, Knoxville, Tenn.

Thin-layer chromatograms (TLC) were obtained on 0.25 mm silica gel 60F-254 plates using 5% ethyl acetate-dichloromethane as the eluent. Preparative layer chromatograms (PLC) were obtained on 20 x 20 x 0.25 cm silica gel GF plates (Analtech, Inc). Column chromatography was performed with silica gel 60, 70-230 mesh (E. Merck). Solvents used for column chromatograms were not usually distilled. Tetrahydrofuran (THF) was dried by distillation over lithium aluminum hydride (LAH). Dioxane was dried by distillation over calcium hydride.

Preparation of lithium diisopropylamide (LDA) was achieved by addition of n-butyl lithium (Aldrich Chem. Co.) to a stirred solution of diisopropylamine in tetrahydrofuran under N_2 at 0°C and cooling the resulting greenish-yellow mixture to -78°C for 10-15 min.

The compounds described in the experimental section are those referred to in Sections IV and V.

1-Hydroxy-2,3-disubstituted naphthalenes (6) (General Procedure); To a stirred solution of LDA at -78°C, prepared from diisopropylamine (771 mg, 7.63 mmol), THF (12 mL) and n-BuLi (4.77 mL, 1.6 M, 7.63 mmol) under N_2 at 0°C, was added a solution of ethyl 2-phenylsulfinylmethylbenzoate (4)[41] (1.00g, 3.47 mmol) in THF (12 mL). The resulting orange-brown anion was stirred at -78°C for 15 min, then 2.4 equivalents of the corresponding Michael acceptor was added neat with washing (THF), into the reaction vessel. The reaction mixture was then brought to room temperature, stirred for 2 h, and finally heated at reflux for 2-3 h. The reaction was quenched by addition of water and the THF was removed under reduced pressure. After acidification with aqueous HCl (10%), the product was extracted with ethyl acetate (2 x 100 mL). The combined ethyl acetate extracts were washed with water, saturated $NaHCO_3$ solution, and brine. The organic solution was dried ($MgSO_4$), filtered, and evaporated to give a brown residue, which was purified by column chromatography (100g, silica gel, benzene) to furnish the corresponding naphthalene.

Ethyl 1-hydroxy-2-naphthoate (6a)[35] from ethyl propenoate; Yield: 28%; colorless crystals from acetone-hexanes; mp 48-49°C (lit.[35] mp 48-49.5°C); ^1H NMR (CCl_4) δ 1.38 (t, J = 7 Hz, 3 H, CH_3), 4.37 (q, J = 7 Hz, 2 H, OCH_2), 7.10 (d, J = 9 Hz, 1 H, ArH), 7.34-7.74 (m, 4 H, ArH), 8.36 (d, J = 7 Hz, 1 H, ArH).

2-Acetyl-1-hydroxynaphthalene (6b)[36] from 3-buten-2-one; Yield: 37%; light yellow solid from benzene-petroleum ether (30-65°); mp 100-101°C (lit.[36] mp 101°C); ^{1}H NMR (CCl_4) δ 2.56 (s, 3 H, $COCH_3$), 7.07 (d, J = 7 Hz, 1 H, ArH), 7.20 - 7.65 (m, 4 H, ArH), 8.28 - 8.46 (d, J = 7 Hz, 1 H, ArH), 13.90 (s, 1 H, ArOH).

Ethyl 1-hydroxy-3-methyl-2-naphthoate (6c)[30] from ethyl trans-2 butenoate; Yield: 57%; colorless crystals; (lit.[30] mp 56-59°C); ^{1}H NMR (CCl_4) δ 1.31 (t, J = 7 Hz, 3 H, CH_3), 2.45 (s, 3 H, $ArCH_3$), 4.28 (q, J = 7 Hz, 2 H, CH_2), 6.83 (s, 1 H, ArH), 7.20 - 7.50 (m, 3 H, ArH), 8.28 (d, J = 7 Hz, 1 H, ArH).

2-Acetyl-1-hydroxy-3-methylnaphthalene (6d) from 3-penten-2-one; Yield: 70%; light yellow crystals from benzene-hexanes; mp 93-93.5°C ^{1}H NMR (CCl_4) δ 2.60 (s, 6 H, $ArCH_3$ and $COCH_3$), 6.89 (s, 1 H, ArH), 7.20-7.56 (m, 3 H, ArH), 8.33 (d, J = 7 Hz, 1 H, ArH), 14.59 (s, 1 H, ArOH).

Ethyl 1-hydroxy-3-methylthiomethyl-2-naphthoate (6e) from ethyl 4-methylthio-trans-2-butenoate; Yield: 64%; colorless crystals; mp 59-60°C; ^{1}H NMR (CCl_4) δ 1.50 (t, J = 7 Hz, 3 H, $CH_2\underline{CH_3}$), 1.89 (s, 3 H, SCH_3), 3.97 (s, 2 H, CH_2S), 4.47 (q, J = 7 Hz, 2 H, $\underline{CH_2}CH_3$), 6.93 (s, 1 H, ArH), 7.30 - 7.62 (m, 3 H, ArH), 8.36 (d, J = 7 Hz, 1 H, ArH), 12.66 (s, 1 H, ArOH).

1,4-Dimethoxy-2,3-disubstituted naphthalenes (10) (General Procedure); To a stirred solution of LDA at -78°C, prepared from diisopropylamine (8.10 mg, 8.03 mmol), THF (12 mL), and n-BuLi (5.02 mL,

1.6 M, 8.03 mmol) under N_2 at 0°C, was added a slurry of 3-phenylsulfonyl-1(3H)-isobenzofuranone (7)[41] (1.00 g, 3.65 mmol) in THF (25mL). To the resulting yellow anion, which partially precipitated, was added 2.4 equivalents of the corresponding Michael acceptor. When the reaction mixture was brought to room temperature, it became yellow to brown in color and solid material appeared. This mixture was stirred for 2 h, and finally heated at reflux for 30 min. The reaction mixture was acidified with aqueous HCl (10%), then evaporated at reduced pressure to remove the THF. The precipitated material was extracted with ethyl acetate (2 x 150 mL), and the combined extracts were washed with water, brine, and aqueous sodium dithionite (3g/50 mL H_2O).

The organic solution was dried ($MgSO_4$), filtered, and evaporated to give a brown residue which was immediately dissolved in acetone (50 mL) and heated at reflux with dimethyl sulfate (1.47 g, 11.64 mmol) and anhydrous K_2CO_3 (2.68 g, 19.4 mmol) overnight. Inorganic material was removed by filtration and the filtrate was evaporated to furnish a brown residue.

In order to remove unreacted dimethyl sulfate, the residue was dissolved in ether (100 mL) and treated with triethylamine (2 mL). After 30 min, the cloudy ether solution was washed with water, aqueous HCl (10%), and brine, then dried ($MgSO_4$), filtered, and evaporated. Final purification of the 1,4-dimethoxy-2,3-disubstituted naphthalenes (10) was accomplished by column chromatography (100g, silica gel, dichloromethane).

Ethyl 1,4-dimethoxy-2-naphthoate (10a) from ethyl propenoate; Yield: 32%; colorless oil; ^{1}H NMR (CCl_4) δ 1.42 (t, J = 7 Hz, 3 H, CH_3), 3.92 (s, 3 H, OCH_3), 3.96 (s, 3 H, OCH_3), 4.38 (q, J = 7 Hz, 2 H, CH_2), 7.05 (s, 1 H, ArH), 7.45 (q, J = 3 Hz, 2 H, ArH), 8.11 (q, J = 3 Hz, 2 H, ArH).

2-Acetyl-1,4-dimethoxynaphthalene (10b) from 3-buten-2-one; Yield: 29%; colorless needles from hexanes; mp 59-60°C; ^{1}H NMR (CCl_4) δ 2.66 (s, 3 H, $COCH_3$), 3.86 (s, 3 H, OCH_3), 3.94 (s, 3 H, OCH_3), 6.97 (s, 1 H, ArH), 7.45 (q, J = 3 Hz, 2 H, ArH), 7.97 - 8.22 (m, 2 H, ArH).

Ethyl 1,4-dimethoxy-3-methyl-2-naphthoate (10c) from ethyl trans-2-butenoate; Yield: 70%; colorless oil; ^{1}H NMR (CCl_4) δ 1.38 (t, J = 7 Hz, 3 H, $CH_2\underline{CH_3}$), 2.32 (s, 3 H, $ArCH_3$), 3.80 (s, 3 H, OCH_3), 3.92 (s, 3 H, OCH_3), 4.38 (q, J = 7 Hz, 2 H, OCH_2), 7.24 - 7.50 (m, 2 H, ArH), 7.92 - 8.14 (m, 2 H, ArH).

2-Acetyl-1,4-dimethoxy-3-methylnaphthalene (10d) from 3-penten-2-one; Yield: 86%; colorless crystals from hexanes; mp 70-72°C; ^{1}H NMR (CCl_4) δ 2.23 (s, 3 H, $ArCH_3$), 2.49 (s, 3 H, $COCH_3$), 3.80 (s, 6 H, 2 OCH_3), 7.33 - 7.48 (m, 2 H, ArH), 7.88 - 8.05 (m, 2 H, ArH).

Ethyl 1,4-dimethoxy-3-methylthiomethyl-2-naphthoate (10e) from ethyl 4-methylthio-trans-2 butenoate; Yield: 28%; colorless oil; ^{1}H NMR (CCl_4) δ 1.41 (t, J = 7 Hz, 3 H, CH_3),1.97 (s, 3 H, SCH_3), 3.89 (s, 3 H, OCH_3), 3.94 (s, 5 H, OCH_3 and CH_2S), 4.38 (q, J = 7 Hz, 2 H, OCH_2), 7.36 - 7.52 (m, 2 H, ArH), 7.90 - 8.12 (m, 2 H, ArH).

3,4-Dihydro-9,10-dimethoxy-(2H)-anthracene-1-one(10f) from 2-cyclohexen-1-one; Yield: 69%, colorless crystals from CH_2Cl_2-hexanes; mp 119-120°C; ^1H NMR (CCl_4) δ 2.06 (m, J = 6 Hz, 2 H, $CH_2CH_2CH_2$), 2.59 (t, J = 7 Hz, 2 H, $COCH_2$), 3.05 (t, J = 7 Hz, 2 H, $ArCH_2$), 3.81 (s, 3 H, OCH_3), 3.92 (s, 3 H, OCH_3),7.28 - 7.60 (m, 2 H, ArH), 7.95 (d, J = 7 Hz, 1 H, ArH), 8.22 (d, J = 7 Hz, 1 H, ArH).

7-Methoxy-3-phenylsulfonyl-1(3H)-isobenzofuranone(11); To a solution of 7-methoxy-3-phenylthio-1(3H)-isobenzofuranone (22)[78] (6.67g, 24.6 mmol) in dichloromethane (300 mL) was added m-chloroperbenzoic acid (10.9g, 54 mmol) and the mixture was stirred at room temperature overnight. The solid m-chlorobenzoic acid was removed by filtration, and the filtrate was washed with aqueous $NaHSO_3$, saturated aqueous $NaHCO_3$, water, and brine. The organic layer was dried ($MgSO_4$), filtered, and evaporated to give a colorless powder which was recrystallized from acetone-hexanes to furnish 7.18 g (96%) of 11 as colorless needles: mp 176-177°C; ^1H NMR ($CDCl_3$) δ 3.93 (s, 3 H, OCH_3), 6.10 (s, 1 H, ArCH), 7.04 (d, J = 8 Hz, 1 H, ArH), 7.40 - 7.92 (m, 7 H, ArH); MS m/e 304 ($M^{+\cdot}$), 163.

Ethyl 3-methyl-1,4,8-trimethoxy-2-naphthoate (12); To a stirred solution of LDA at -78°C, prepared from diisopropylamine (0.73 g, 7.24 mmol), THF (12 mL), and n-BuLi (4.53 mL, 1.6 M, 7.24 mmol) under N_2 at 0°C, was added a slurry of sulfone 11 (1.00 g, 3.29 mmol) in THF (12 mL) and the mixture was stirred at -78°C for 15 min. Ethyl trans-2-butenoate (2) (0.90g, 7.9 mmol) was added to the deep-yellow anion solution. The cooling bath was immediately removed and the mixture

was brought to room temperature. After stirring the mixture for 2 h, it was heated at reflux for an additional 2 h. The reaction mixture was acidified with glacial acetic acid and the THF was removed under reduced pressure. The residue was dissolved in ethyl acetate (200 mL) and washed with water, aqueous sodium dithionite (2g/50 mL H_2O), and brine. The organic extract was dried ($MgSO_4$), filtered, and evaporated to give a brown solid.

The crude product was dissolved in acetone (30 mL) and heated under reflux with dimethyl sulfate (1.3g, 10.3 mmol) and anhydrous K_2CO_3(2.50g, 18.20 mmol) overnight. Inorganic material was removed by filtration and the filtrate was evaporated to give a brown oil which was dissolved in ether (100mL) and treated with triethylamine (2mL). After standing for 30 min, the ether solution was washed with water, aqueous HCl(10%) and brine, then dried ($MgSO_4$), filtered, and evaporated to give an oil which was further purified by column chromatography (100g, silica gel, CH_2Cl_2) to furnish 730 mg (73%) of 12 as a colorless oil: ^1H NMR (CCl_4) δ 1.40 (t, J = 7 Hz, 3 H, $CH_2\underline{CH_3}$), 2.28 (s, 3 H, $ArCH_3$), 3.76 (s, 3 H, OCH_3), 3.79 (s, 3 H, OCH_3), 3.92 (s, 3 H, OCH_3), 4.37 (q, J = 7 Hz, 2 H, OCH_2), 6.74 (d, J = 7 Hz, 1 H, ArH), 7.30 (t, J = 7 Hz, 1 H, ArH), 7.60 (d, J = 7 Hz, 1 H, ArH).

Methyl 4,6-dimethoxy-2-phenylsulfinylmethylbenzoate (13); To a solution of methyl 4,6-dimethoxy-2-phenylthiomethylbenzoate[79](140 mg, 0.44mmol) in dichloromethane (10mL), cooled to -78°C was added a solution of m-chloroperbenzoic and (85%) (144 mg, 0.44 mmol) in dichloromethane (5 mL). The reaction mixture was stirred at -78°C for 1 h and slowly warmed to room temperature. Tlc analysis at this point indicated that the reaction produced a new product and that the starting material

was almost completely consumed. To the resulting product was added 5 mL of aqueous sodium bisulfite (300 mg, 2.88 mmol) and the mixture was stirred for 10 min. The dichloromethane layer was separated and washed with aqueous $NaHCO_3$, water, and brine. The organic solution was dried ($MgSO_4$), filtered, and evaporated to give an oil which was purified by column chromatography (35 g, silica gel, CH_2Cl_2 to 15% $EtOAc/CH_2Cl_2$) to furnish 132 mg (90%) of sulfoxide 13 as a colorless oil: ^1H NMR ($CDCl_3$) δ 3.60 (s, 3 H, OCH_3), 3.70 (s, 3 H, OCH_3), 3.78 (s, 3 H, OCH_3), 4.07 (s, 2 H, $\underline{CH_2}Ar$), 6.09 (d, J = 2.4 Hz, 1 H, ArH), 6.38 (d, J = 2.4 Hz, 1 H, ArH), 7.44 (br s, 5 H, ArH).

Methyl 6,8-dimethoxy-1-hydroxy-3-methyl-2-naphthoate (15); To a stirred solution of LDA at -78°C, prepared from diisopropylamine (67 mg, 0.66 mmol), THF (7 mL), and n-BuLi(0.41 mL, 1.6M, 0.66 mmol) was added sulfoxide 13 (100 mg, 0.3 mmol) dissolved in THF (15 mL). To the resulting yellow-brown anion was added methyl trans-2-butenoate (14) (72 mg, 0.72 mmol) in THF (7 mL). The reaction mixture was held at -78°C for 10 min then brought to room temperature, stirred for 2 h, and finally heated at reflux for 2 h. The brown solution was neutralized with glacial acetic acid and the THF was removed under reduced pressure. The residual material was dissolved in ethyl acetate (75 mL) and the solution was washed with water, saturated aqueous $NaHCO_3$ and brine, then dried ($MgSO_4$), filtered, and evaporated to give a brown residue which was purified by column chromatography to give 55 mg (60%) of 15 as a solid. Recrystallization of the product from dichloromethane-petroleum ether (30-65°) provided colorless crystals: mp 84-86°C; ^1H NMR ($CDCl_3$) δ 2.32 (s, 3 H, $ArCH_3$), 3.74 (s, 3 H, OCH_3), 3.83

(s, 3 H, OCH_3), 3.85 (s, 3 H, OCH_3), 6.29 (d, J = 2.4 Hz, 1 H, ArH), 6.46 (d, J = 2.4 Hz, 1 H, ArH), 6.84 (s, 1 H, ArH), 10.58 (s, 1 H, ArOH).

Ethyl 2-hydroxy-6-methylbenzoate (18)[43]; Compound 18 was prepared as described[43] by condensation of ethyl acetoacetate (195g, 1.5 mol) with crotonaldehyde (105g, 1.5 mol) to give ethyl 6-carboxy-5-methyl-2-cyclohexen-1-one, which was aromatized by treatment with Br_2/HOAc; mp 41-42°C; (lit.[43] 43-44°C); ^1H NMR (CCl_4) δ 1.44 (t, J = 8 Hz, 3 H, $CH_2\underline{CH_3}$), 2.53 (s, 3 H, $ArCH_3$), 4.40 (q, J = 8 Hz, 2 H, $\underline{CH_2}CH_3$), 6.59 (d, J = 8 Hz, 1 H, ArH), 6.74 (d, J = 8 Hz, 1 H, ArH), 7.18 (t, J = 8 Hz, 1 H, ArH).

Ethyl 2-methoxy-6-methylbenzoate (19); A mixture of ethyl 2-hydroxy-6-methylbenzoate (18) (85.6 g, 0.49 mol), dimethyl sulfate (72 g, 0.57 mol), and anhydrous potassium carbonate (100g, 0.71 mol), in acetone (200 mL) was heated at reflux under nitrogen with vigorous stirring for 3 days. Inorganic material was removed by filtration and the filtrate was evaporated under reduced pressure to give an oil. The residual oil was dissolved in ether (250 mL) and treated with triethylamine (30 mL) for 30 min. The ether solution was washed with water, 10% aqueous HCl, and brine, then dried ($MgSO_4$), filtered, and evaporated to give an oil. Final purification was accomplished by distillation (bp 110-115°C/2.5-3.5 mm) to furnish 78.1 g (85%) of 19 as a colorless oil: (lit.[43] bp 80°C at 0.8 mm); ^1H NMR (CCl_4) δ 1.35 (t, J = 7 Hz, 3 H, $CH_2\underline{CH_3}$), 2.26 (s, 3 H, $ArCH_3$), 3.76 (s, 3 H, OCH_3), 4.30 (q, J = 7 Hz, 2 H, OCH_2), 6.66 (d, J = 8 Hz, 1 H, ArH), 6.70 (d, J = 8 Hz, 1 H, ArH), 7.13 (t, J = 8 Hz, 1 H, ArH).

Ethyl 2-dibromomethyl-6-methoxybenzoate(20); A mixture of ethyl 2-methoxy-6-methylbenzoate (19) (2.0g, 10.3 mmol) and N-bromosuccinimide (NBS) (3.80 g, 21.4 mmol) in CCl_4 (200 mL) was heated at reflux under N_2 with irradiation by a sunlamp for 30 min. A catalytic amount of benzoyl peroxide was added and heating was continued with irradiation. The course of the reaction was followed by ^1H NMR. The stepwise disappearance of the aromatic methyl and methylene absorptions at δ 2.26 and 3.89, respectively and the concomittant appearance of a singlet at δ 6.76 indicated the reaction was complete. The reaction mixture was then cooled in an ice bath and filtered to remove succinimide. Evaporation of the solvent furnished crude dibromo compound 20, which was not purified but was hydrolyzed directly: ^1H NMR (CCl_4) δ 1.39 (t, J = 8 Hz, 3 H, $CH_2\underline{CH_3}$), 3.81 (s, 3 H, OCH_3), 4.37 (q, J = 8 Hz, 2 H, OCH_2), 6.76 (s, 1 H, $CHBr_2$), 6.80 (d, J = 8 Hz, 1 H, ArH), 7.37 (t, J = 8 Hz, 1 H, ArH), 7.56 (d, J = 8 Hz, 1 H, ArH).

7-Methoxy-3-hydroxy-1(3H)-isobenzofuranone(21); A mixture of dibromomethyl benzoate 20 (15 g, 42.6 mmol), 9% HCl (160 mL), and enough acetic acid to make the mixture homogeneous was heated at reflux for 4 h. The solution was evaporated to dryness under reduced pressure and the residue was dissolved in ethyl acetate (350 mL). The ethyl acetate solution was extracted repeatedly with saturated aqueous $NaHCO_3$ (3 x 150 mL) and the combined sodium bicarbonate extract were acidified with 10% aqueous HCl. The organic material was extracted with ethyl acetate (350 mL) and washed with water and brine. The ethyl acetate solution was dried ($MgSO_4$), filtered, and evaporated to give 2.76 g of 21 as a colorless solid.

The ethyl acetate layer separated earlier from sodium bicarbonate solution was dried ($MgSO_4$), and evaporated to dryness. The residue containing the starting material was further hydrolyzed as described above to furnish an additional 3.77 g of 21 (total yield, 80%): mp 152-154°C: ^1H NMR (Acetone-d_6) δ 2.93 (s, 3 H, OCH_3), 6.54 (d, J = 8 Hz, 1 H, CHOH), 6.82 (d, J = 8 Hz, 1 H, CHOH), 7.14 (d, J = 8 Hz, 1 H, ArH), 7.18 (d, J = 7 Hz, 1 H, ArH), 7.70 (t, J = 8 Hz, 1 H, ArH).

7-Methoxy-3-phenylthio-1(3H)-isobenzofuranone(22); A mixture of 7-methoxy-3-hydroxy-1(3H)-isobenzofuranone (21) (6.13g, 34 mmol), benzenethiol (4.89 g, 44.5 mmol), and benzene (400 mL) was heated at reflux with a catalytic amount of p-toluenesulfonic acid for 3 h. The water generated in the reaction was azeotropically removed using a Dean-Stark apparatus. The benzene was evaporated under reduced pressure and the residual oil was dissolved in ethyl acetate (300 mL), and washed successively with water, saturated aqueous $NaHCO_3$, and brine. The ethyl acetate solution was dried ($MgSO_4$), filtered, and evaporated to furnish a pale-yellow solid which was purified by column chromatography (100 g, silica gel, CH_2Cl_2) to give 6.67 g (72%) of 22 as a white powder: mp 126-127°C; ^1H NMR (Acetone-d_6) δ 3.88 (s, 3 H, OCH_3), 6.88 (s, 1 H, PhSCH), 7.12 (t, J = 8 Hz, 1 H, ArH), 7.24-7.60 (m, 6 H, ArH), 7.72 (t, J = 8 Hz, 1 H, ArH).

Methyl 3-methyl-1,4,8-trimethoxy-2-naphthoate(23); Preparation of 23 was accomplished from 7-methoxy-3-phenylsulfonyl-1(3H)-isobenzofuranone (11)(4.0g, 13 mmol) and methyl trans-2-butenoate(14) (3.16g, 31.6 mmol) by the method described for preparation of 12. The yield

of 23, a colorless oil, was 83%; ^{1}H NMR (CCl_4) δ 2.29 (s, 3 H, $ArCH_3$), 3.77 (s, 3 H, OCH_3), 3.79 (s, 3 H, OCH_3), 3.89 (s, 3 H, OCH_3), 3.92 (s, 3 H, OCH_3), 6.74 (d, J = 8 Hz, 1 H, ArH), 7.29 (t, J = 8 Hz, 1 H, ArH), 7.59 (d, J = 8 Hz, 1 H, ArH).

Methyl 3-bromomethyl-1,4,8-trimethoxy-2-naphthoate (24a); A mixture of methyl 3-methyl-1,4,8-trimethoxy-2-naphthoate (23) (3.12 g, 10.76 mmol), N-bromosuccinimide (2.04g, 11.0 mmol), and carbon tetrachloride (300 mL) was heated at reflux for 30 min while irradiated with a sunlamp. A catalytic amount of benzoyl peroxide was added and the mixture was heated at reflux with irradiation for an additional 1.5 h. The reaction mixture was refrigerated, then filtered to remove succinimide. The filtrate was evaporated under reduced pressure to give a solid which was further purified by column chromatography (100g, silica gel, 5% EtOAc-CH_2Cl_2) to furnish 3.33g (84%) of 24a as a light yellow solid: mp 84-87°C; ^{1}H NMR (CCl_4) δ 3.80 (s, 3 H, OCH_3), 3.92 (s, 3 H, OCH_3), 3.94 (s, 3 H, OCH_3), 3.98 (s, 3 H, OCH_3), 4.73 (s, 3 H, CH_2Br), 6.81 (d, J = 8 Hz, 1 H, ArH), 7.33 (t, J = 8 Hz, 1 H, ArH), 7.60 (d, J = 8 Hz, 1 H, ArH).

Ethyl 3-bromomethyl-1,4,8-trimethoxy-2-naphthoate (24b); Preparation of 24b was achieved from 12 by the procedure employed for the preparation of 24a. Compound 24b, a colorless solid, was obtained in 81% yield; mp 61-63°C; ^{1}H NMR (CCl_4) δ 1.44 (t, J = 7 Hz, 3 H, $CH_2\underline{CH_3}$) 3.79 (s, 3 H, OCH_3), 3.93 (s, 3 H, OCH_3), 3.99 (s, 3 H, OCH_3), 4.43 (q, J = 7 Hz, 2 H, $\underline{CH_2}CH_3$), 4.73 (s, 2 H, CH_2Br), 6.82 (d, J = 7 Hz, 1 H, ArH), 7.34 (t, J = 7 Hz, 1 H, ArH), 7.62 (d, J = 7 Hz, 1 H, ArH).

Methyl 3-phenylthiomethyl-1,4,8-trimethoxy-2-naphthoate (25a);

To a solution of sodium ethoxide, prepared by dissolving sodium (0.23 g, 9.93 mmol) in absolute ethanol (75 mL), was added benzenethiol (1.24 g, 10.93 mmol), and the mixture was stirred for 10 min. A solution of 24a (3.33g, 9.02 mmol) in THF (50 mL) was added to the thiophenoxide solution which was then heated at reflux overnight. The resulting dark solution was acidified with 10% aqueous HCl and the ethanol was removed under reduced pressure. The deposited material was dissolved in ethyl acetate (200 mL) and the extract was washed successively with 10% NaOH, 10% HCl, water, and brine. The organic solution was dried ($MgSO_4$), filtered, and evaporated to give a brown oil, which upon chromatographic separation (100 g, silica gel, CH_2Cl_2 to 5% EtOAc-CH_2Cl_2), furnished 3.42 g (75%) of 25a as a light yellow solid. Recrystallization of the material from ethanol provided colorless needles: mp 91-92°C; ^1H NMR (CCl_4) δ 3.78 (s, 6 H, 2 OCH_3), 3.83 (s, 3 H, OCH_3), 3.90 (s, 3 H, OCH_3), 4.34 (s, 2 H, $PhSCH_2$), 6.76 (d, J = 8 Hz, 1 H, ArH), 7.08 - 7.44 (m, 6 H, ArH), 7.56 (d, J = 8 Hz, 1 H, ArH).

Ethyl 3-phenylthiomethyl-1,4,8-trimethoxy-2-naphthoate (25b);

Preparation of 25b was accomplished from 24b by the same method described for preparation of 25a. The solid was recrystallized from MeOH-H_2O to give a 98% yield of 25b as colorless needles: mp 81°C; ^1H NMR (CCl_4) δ 1.36 (t, J = 7 Hz, 3 H, CH_2CH_3), 3.80 (s, 6 H, 2 OCH_3), 3.90 (s, 3 H, OCH_3), 4.33 (q, J = 7 Hz, 2 H, CH_2CH_3), 4.36 (s, 2 H, $PhSCH_2$), 6.76 (d, J = 8 Hz, 1 H, ArH), 7.04 - 7.50 (m, 6 H, ArH), 7.56 (d, J = 8 Hz, 1 H, ArH); MS m/e 412 ($M^{+\cdot}$), 367, 303.

Methyl 3-phenylsulfinylmethyl-1,4,8-trimethoxy-2-naphthoate (26a); Sulfoxide 26a was prepared from sulfide 25a by oxidation with either sodium metaperiodate (method A) or m-chloroperbenzoic acid (method B).

Method A: To a solution of sulfide 25a (3.4g, 8.55 mmol) in methanol, was added an aqueous solution of $NaIO_4$(2.38g, 11.1 mmol, 50 mL H_2O). The mixture was stirred at room temperature for 2 days at which time tlc analysis indicated that the starting material was consumed.

The insoluble inorganic material was removed by filtration and the solid was washed with methanol. The filtrate and methanol washings were combined and evaporated under reduced pressure to give a residue which was dissolved in ethyl acetate (200 mL). The ethyl acetate solution was washed with water and brine, then dried ($MgSO_4$), filtered, and evaporated to give a solid which was purified by column chromatography (100g, silica gel, 10 to 15% EtOAc-CH_2Cl_2) to give 3.36 g (95%) of 26a as colorless crystals: mp 114-116°C; ^1H NMR (CCl_4) δ 3.83 (s, 3 H, OCH_3), 3.93 (s, 6 H, 2 OCH_3), 3.95 (s, 3 H, OCH_3), 4.08 (d, J = 13 Hz, 1 H, CH(H)SOPh), 4.40 (d, J = 13 Hz, 1 H, CH(H)SOPh), 6.83 (d, J = 7 Hz, 1 H, ArH), 7.30 - 7.70 (m, 7 H, ArH); MS m/e 414 ($M^{+\cdot}$).

Method B: To a solution of 25a (5.24g, 13.2 mmol) in dichloromethane (300 mL), cooled to -78°C, was added m-chloroperbenzoic acid (2.70g, 13.2 mmol). The mixture was maintained at -78°C for 30 min, then slowly brought to room temperature. An additional quantity (270 mg) of m-chloroperbenzoic acid was added to the mixture since a substantial amount of the starting material had not reacted.

The reactions mixture was stirred for another 5 min at room temperature, then quenched with aqueous $NaHSO_3$ solution (2g, 75 mL H_2O). Tlc analysis of the reaction mixture indicated a small amount of less polar sulfone 26c (Rf=0.31) had formed along with the desired sulfoxide 26a (Rf=0.16). The dichloromethane layer was separated from the aqueous layer, then washed successively with aqueous $NaHCO_3$, water, and brine. The organic solution was dried ($MgSO_4$), filtered and evaporated to give a foam, which furnished upon chromatographic separation (100g, silica gel, 5 to 30% EtOAc-CH_2Cl_2), 4.80 g (88%) of 26a and 0.51 g (9%) of methyl 3-phenylsulfonylmethyl-1,4,8-trimethoxy-2-naphthoate (26c). Compound 26a, prepared by this procedure, was identical with the sample prepared by method A. Recrystallization of 26c from acetone-hexanes provided colorless plates: mp 142-143°C; ^{1}H NMR ($CDCl_3$)δ 3.76 (s, 3 H, OCH_3), 3.82 (s, 3 H, OCH_3), 3.91 (s, 3 H, OCH_3), 3.94 (s, 3 H, OCH_3), 4.84 (s, 2 H, SO_2CH_2), 6.90 (d'd, J = 7 and 2 Hz, 1 H, ArH), 7.27 - 7.60 (m, 6 H, ArH), 7.79 (d'd, J = 7 and 2 Hz, 1 H, ArH).

Ethyl 3-phenylsulfinylmethyl-1,4,8-trimethoxy-2-naphthoate (26b); Preparation of 26b was achieved in quantitative yield from 25b using method A (above). Recrystallization of the product from acetone-hexanes provided 26b as colorless crystals: mp 104-107°C; ^{1}H NMR (CCl_4) δ 1.48 (t, J = 7 Hz, 3 H, $CH_2\underline{CH_3}$), 3.83 (s, 3 H, OCH_3), 3.92 (s, 3 H, OCH_3), 3.94 (s, 3 H, OCH_3), 4.10 (d, J = 13 Hz, 1 H, $\underline{CH}$(H)SOPh), 4.40 (d, J = 13 Hz, 1 H, CH($\underline{H}$)SOPh), 6.80 (d, J = 7 Hz, 1 H, ArH), 7.30 - 7.66 (m, 7 H, ArH).

2-Acetyl-1-hydroxy-3-methyl-8,9,10-trimethoxyanthracene (27): To a stirred solution of LDA at -78°C, prepared from diisopropylamine (1.69g, 16.7 mmol), THF (40 mL), and n-BuLi (10.3 mL, 1.6 M, 16.5 mmol) under N_2 at 0°C for 15 min, was added a solution of sulfoxide 26a (3.0g, 7.24 mmol) in THF (40 mL). To the resulting brown anion solution was added 3-penten-2-one (1.8 g, 21.4 mmol), with THF washing. The reaction was stirred at -78°C for 15 min, then brought to room temperature and after 2.5 h, heated at reflux overnight. The brown-red reaction mixture was acidified with glacial acetic acid and the THF was removed under reduced pressure to give an oil which was dissolved in ethyl acetate (200 mL). The ethyl acetate solution was washed with water and brine, then dried ($MgSO_4$), filtered, and evaporated to furnish an oil. The oil gave, upon chromatographic separation (100g, silica gel, CH_2Cl_2), 3.4g (71%) of 27 as a yellow solid. Compound 27 was labile and underwent decomposition to give anthraquinone 30 at room temperature. Recrystallization of the unstable product from acetone-hexanes provided analytically pure 27 as brown crystals: mp 132-134°C; IR (Nujol) 2940, 2860, 1700, 1630, 1554 cm^{-1}; UV (EtOH) λ max 267; ^1H NMR (CCl_4) δ 2.43 (s, 3 H, $ArCH_3$), 2.59 (s, 3 H, $COCH_3$), 3.96 (s, 6 H, 2 OCH_3), 3.99 (s, 3 H, OCH_3), 6.66 (d, J = 8 Hz, 1 H, ArH), 7.25 (t, J = 8 Hz, 1 H, ArH), 7.39 (s, 1 H, ArH); MS m/e 340 ($M^{+\cdot}$), 325, 311; Anal. Calcd for $C_{20}H_{20}O_5$: C, 70.57; H, 5.92; Found: C, 70.68; H, 6.07.

2-Acetyl-8,9-dimethoxy-10-ethoxy-1-hydroxy-3-methylanthracene (28a); To a stirred solution of LDA at -78°C, prepared from diisopropylamine (0.5 g, 4.92 mmol), THF (15 mL), and n-BuLi (3.92 mL, 1.6 M, 5.26 mmol), was added a solution of sulfoxide 26b (1.04 g, 2.40 mmol) in THF

(7 mL). The resulting brown anion was allowed to react with 3-penten-2-one (0.46g, 5.46 mmol) at -78°C for 10 min, then permitted to warm to room temperature. The mixture was stirred at room temperature for 2 h, then heated at reflux overnight. Tlc analysis of the reaction mixture indicated that two new products (Rf = 0.70 and 0.60) had formed with ca 30% of the starting material remaining unreacted. The reaction mixture was cooled to room temperature and acidified with glacial acetic acid. The mixture was evaporated at reduced pressure to remove THF and the residue was extracted with ethyl acetate (2 x 100 mL). The combined ethyl acetate extracts were washed with water and brine, then dried ($MgSO_4$), filtered, and evaporated to give a yellow-orange solid. Further purifiation was accomplished by column chromatography (100g, silica gel, C_6H_6 to 15% EtOAc-CH_2Cl_2) to give 320 mg (39%) of 27 and 220 mg (23%) of 28a as a yellow solid: mp 114-117°C; ^1H NMR (CCl_4) δ 1.54 (t, J = 7 Hz, 3 H, $CH_2\underline{CH_3}$), 2.42 (s, 3 H, $ArCH_3$), 2.60 (s, 3 H, $COCH_3$), 3.96 (s, 6 H, 2 OCH_3), 6.65 (d, J = 8 Hz, 1 H, ArH), 7.23 (t, J = 8 Hz, 1 H, ArH), 7.38 (s, 1 H, ArH), 7.64 (d, J = 8 Hz, 1 H, ArH), 10.95 (s, 1 H, ArOH); MS m/e 354 ($M^{+\cdot}$), 339, 310, 295. Compound 28a was labile and underwent decomposition at room temperature to give anthraquinone 30.

2-Acetyl-9-n-butyl-8,9-dimethoxy-1-hydroxy-3-methyl-10(9H) anthracenone (29); To a stirred solution of LDA at -78°C, prepared from diisopropylamine (0.54g, 5.32 mmol), THF (40 mL), and an excess n-BuLi (3.50 mL, 1.6 M, 5.60 mmol) under N_2 at 0°C, was added a solution of 26a (1.00g, 2.42 mmol) in THF (15 mL). The resulting brown anion was allowed to react with 3-penten-2-one (0.63g, 7.45 mmol) at -78°C for 15 min, then the reaction mixture was brought slowly to room temperature,

and after 2 h, heated at reflux overnight. Tlc analysis of the reaction indicated that two new products (Rf = 0.65 and 0.60) had formed and that a substantial amount of unreacted starting material was present. Workup was performed by the procedure described for 27. Chromatographic separation (100g, silica gel, benzene to 15% EtOAc-CH_2Cl_2) of the crude product furnished 0.47 g (57.5%) of 27 and 0.20 g (22.4%) of the assigned anthrone 29 as a yellow solid. Attempts to obtain a pure sample of the assigned anthrone 29 by recrystallization were not successful since the product was extremely labile and underwent decomposition at 0°C to a mixture of products which could not be characterized: ^{1}H NMR (CCl_4) δ 0.93 (t, J = 8 Hz, 3 H, $CH_2\underline{CH_3}$), 1.00 - 1.30 (m, 6 H, $(CH_2)_3$), 2.60 (s, 3 H, $ArCH_3$), 2.56 (s, 3 H, $COCH_3$), 3.92 (s, 6 H, 2 OCH_3), 6.61 (d, J = 8 Hz, 1 H, ArH), 7.20 (t, J = 8 Hz, 1 H, ArH), 7.34 (s, 1 H, ArH), 7.70 (d, J = 8 Hz, 1 H, ArH), 10.92 (s, 1 H, ArOH); MS m/e 382 ($M^{+\cdot}$), 325, 311, 295.

2-Acetyl-1-hydroxy-8-methoxy-3-methylanthraquinone (30); Anthraquinone 30 was obtained by separating the decomposed products of anthracenes 27 and 28a at room temperature using a preparative tlc plate developed with 3% ethyl acetate-dichloromethane. The material obtained was an orange-red powder: mp 232-234°C; ^{1}H NMR ($CDCl_3$) δ 2.37 (s, 3 H $ArCH_3$), 2.60 (s, 3 H, $COCH_3$), 4.06 (s, 3 H, OCH_3), 7.36 (d, J = 8 Hz, 1 H, ArH), 7.60 (s, 1 H, ArH), 7.74 (t, J = 8 Hz, 1 H, ArH), 7.95 (d, J = 8 Hz, 1 H, ArH), 13.22 (s, 1 H, ArOH); MS m/e 310 ($M^{+\cdot}$), 295.

1-Hydroxy-3-methyl-2(4'-methyl-hexa-2'(E),4'(E)-dienoyl)-8,9,10-trimethoxyanthracene (32); Lithium diisopropylamide was prepared by stirring a mixture of diisopropylamine (173 mg, 1.71 mmol), THF (7 mL), and n-BuLi (1 mL, 1.6 M, 1.6 mmol) under N_2 at 0°C for 15 min. To the pale greenish-yellow solution, cooled to -78°C, was added a solution of 27 (253 mg, 0.74 mmol) in THF (7 mL) and the mixture was stirred at -78°C for 5 min. To the dark red anion solution was added tiglaldehyde (31) (173 mg, 2.06 mmol) and the reaction mixture was brought to room temperature. The resulting red solution was stirred at room temperature for 4 h, then acidified with glacial acetic acid. The THF was removed under reduced pressure, and the residual mixture was dissolved in ethyl acetate (100 mL), which was washed with water and brine, then dried ($MgSO_4$), filtered and evaporated to give a red foam. Purification of crude dieneone 32 was accomplished by column chromatography (15 g, silica gel, benzene to 15% EtOAc-CH_2Cl_2) to yield 227 mg (75%) of 32 as a red-brown solid. Recrystallization of the material from acetone-hexanes gave pure 32 as yellow-orange needles: mp 154-155.5°C; UV (EtOH) λ max 228 (14000), 262 (82000), 293 (3200), 387 (10600), 418 (6000) nm; ^1H NMR (CCl_4) δ 1.80 (d, J = 7 Hz, 3 H, =CH$\underline{CH_3}$), 1.85 (s, 3 H, =CCH_3), 2.48 (s, 3 H, ArCH_3), 3.94 (s, 3 H, OCH_3), 3.97 (s, 6 H, 2 OCH_3), 5.86 (q, J = 7 Hz, 1 H, =$\underline{CH}CH_3$), 6.40 (d, J = 15 Hz, 1 H, COCH=$\underline{CH}$), 6.65 (d, J = 8 Hz, 1 H, ArH), 6.98 (d, J = 15 Hz, 1 H, COCH=$\underline{CH}$), 7.23 (t, J = 8 Hz, 1 H, ArH), 7.74 (d, J = 8 Hz, 1 H, ArH), 10.36 (s, 1 H, ArOH); MS m/e 406 ($M^{+\cdot}$), 391, 310, 295; Anal. Calcd for $C_{25}H_{26}O_5$: C, 73.87; H, 6.45; Found: C, 73.69; H, 6.55.

5-Methyl-2(1'-methyl-1'(E)-propenyl)-7,11,12-trimethoxy-4H-anthra[1,2-*b*]pyran-4-one (33); To a solution of o-hydroxy dienone 32 (472 mg, 1.16 mmol) in t-amyl alcohol (10 mL) was added SeO_2 (192 mg, 1.73 mmol) and the mixture was heated under N_2 at 60-70°C overnight. The resulting dark product was filtered through a celite pad and the filtrate was evaporated under reduced pressure to give a dark residue. Chromatographic separation (50g, silica gel, CH_2Cl_2 to 10% EtoAc-CH_2Cl_2) of the residue yielded 129 mg (27%) of 33 as a yellow solid, 47 mg (10%) of 34, 56.8 mg (13%) of 35, and 236 mg (50%) of the unreacted starting material 32. The recovered starting material was transformed to give an additional 26 mg (total yield of 33%) of 33. Recrystallization of the chromatographed sample of 33 from ethanol provided yellow needles: mp 150.5 - 152.5°C; UV (EtOH) λ max 245 (33000), 264 (78000), 295 (17000), 390 (9800)nm; ^1H NMR ($CDCl_3$) δ 1.98 (d, J = 7 Hz, 3 H, $CH\underline{CH_3}$), 2.02 (s, 3 H, CCH_3), 2.98 (s, 3 H, $ArCH_3$), 3.88 (s, 3 H, OCH_3), 4.03 (s, 3 H, OCH_3), 4.08 (s, 3 H, OCH_3), 6.46 (s, 1 H, COCH), 6.84 (d, J = 8 Hz, 1 H, ArH), 7.80 (s, 1 H, ArH), 7.88 (d, J = 8 Hz, 1 H, ArH); MS m/e 404 ($M^{+\cdot}$), 389, 309, 295; Anal. Calcd for $C_{25}H_{24}O_5$: C, 74.25; H, 5.89; Found: C, 74.28; H, 5.98.

11-Methoxy-5-methyl-2(1'-methyl-1'(E)-propenyl)-4H-anthra[1,2-*b*]pyran-4,7,12-trione(16c); To a solution of 33 (336 mg, 0.83 mmol) in dioxane (50 mL) was added AgO (415 mg, 3.35 mmol) forming a suspension which was stirred at room temperature. To the stirred mixture was added 4 N HNO_3 until the silver oxide completely dissolved. The resulting colorless solution was stirred for 5 min, then diluted with a mixture of $CHCl_3$ and H_2O (4:1) (200 mL). The organic layer was washed

with water and brine, then dried ($MgSO_4$), filtered and evaporated under reduced pressure to give 314 mg of a yellow solid. Recrystallization of the solid material from dichloromethane-hexanes (3 times) provided 258 mg (83%) of analytically pure 16c as yellow needles: mp 251-252°C; UV (EtOH) λ max 216 (27000), 237 (33800), 268 (28000), 320 (5900), 384 (7500) nm; ^1H NMR ($CDCl_3$) δ 2.10 (s, 3 H, CCH_3), 2.04 (d, J = 7 Hz, $CHCH_3$), 2.98 (s, 3 H, $ArCH_3$), 4.05 (s, 3 H, OCH_3), 6.35 (s, 1 H, COCH), 7.20 - 7.50 (m, 1 H, CH_3CH), 7.44 (d, J = 8 Hz, 1 H, ArH), 7.91 (s, 1 H, ArH); MS m/e 374 ($M^{+\cdot}$), 295, 266; Anal. Calcd for $C_{23}H_{18}O_5$: C, 73.79; H, 4.85; Found: C, 73.50; H, 4.95.

5-Methyl-2(1'-methyl-1'(E)-propenyl)-7,11,12-trimethoxy-2,3-dihydro-4H-anthra[1,2-*b*]pyran-4-one(34);

Method A: To a solution of 32 (127 mg, 0.31 mmol) in methanol (20 mL) was added aqueous sodium acetate (240 mg in 2 mL of H_2O) and the mixture was heated at reflux under N_2 for 40 h. Tlc analysis of the reaction during this period showed that a highly fluorescent compound, less polar than the starting material, had formed along with several other minor components and that a substantial amount of unreacted starting material remained. Since further heating did not alter the extent of reaction, the solution was cooled and diluted with ethyl acetate (100 mL). The ethyl acetate solution was washed with water and brine, then dried ($MgSO_4$), filtered, and evaporated to give a pale yellow oil, which upon chromatographic separation (35g, silica gel, CH_2Cl_2) furnished 44 mg (35%) of 34 as an orange solid and 52 mg (41%) of unreacted starting material. The recovered starting material was transformed to provide an additional 19 mg of 34, which increased the total yield of

the cyclized product to 50%. Recrystallization of the product from benzene-petroleum ether (30-65°) furnished pure 34 as an orange solid: mp 129-131°C: ^{1}H NMR ($CDCl_3$) δ 1.75 (d, J = 7 Hz, 3 H, = $CH\underline{CH}_3$), 1.92 (s, 3 H, = CCH_3), 2.64 (d'd, J = 16 and 4 Hz, 1 H, $COCH_e$), 2.78 (s, 3 H, $ArCH_3$), 3.06 (d'd, J = 16 and 14 Hz, 1 H, $COCH_a$), 3.85 (s, 3 H, OCH_3), 3.97 (s, 3 H, OCH_3), 4.01 (s, 3 H, OCH_3), 4.97 (d'd, J = 14 and 4 Hz, 1 H, $O\underline{CH}CH_2$), 5.82 (q, J = 7 Hz, 1 H, $\underline{CH}CH_3$) 6.76 (d, J = 8 Hz, 1 H, ArH), 7.40 (d, J = 8 Hz, 1 H, ArH), 7.49 (s, 1 H, ArH), 7.80 (d, J = 8 Hz, 1 H, ArH). MS m/e 406 ($M^{+\cdot}$), 391, 324, 310.

Method B: To a solution of 32 (30 mg, 0.074 mmol) in methanol (5 mL) was added a 2% KOH solution (6.2 mg, 0.11 mmol), and the resulting red mixture was heated on a steam bath for 5 min. The reaction mixture was then quenched immediately with glacial acetic acid and diluted with ethyl acetate (50 mL). The ethyl acetate layer was separated and washed with water and brine, then dried ($MgSO_4$), filtered and evaporated to give a deep-red residue. The residue was chromatographically separated (25g, silica gel, CH_2Cl_2) to yield 3.0 mg (10%) of 34. No starting material was recovered from the column separation. The product obtained was identical with that prepared by method A.

Method C: The compound 34 was obtained in 10% yield as a side-product when compound 32 was heated in t-amyl alcohol at reflux in the presence of SeO_2 to yield dehydrocyclization product 33.

1-Hydroxy-8-methoxy-3-methyl-2-(4'-methyl-hexa-2'(E),4'(E)-dienoyl)anthraquinone(35);

Method A: A mixture of 32 (21.8 mg, 0.054 mmol), pyridine (3 mL) and water (2 mL) was stirred at room temperature overnight. The red reaction was acidified with cold 10% HCl, then dissolved in ethyl acetate (50 mL). The ethyl acetate solution was washed with water and brine, then dried (Na_2SO_4), filtered, and evaporated under reduced pressure to give a brown residue. Column chromatography (10 g, silica gel, CH_2Cl_2) of the residue furnished 11.3 mg (56%) of 35 as a brown solid. Recrystallization of the product from ethanol-hexanes provided a pure sample of 35 as red-brown needles: mp 140-142°C; ^1H NMR ($CDCl_3$) δ 1.81 (d, J = 7 Hz, 3 H, $CH\underline{CH_3}$), 1.83 (s, 3 H, CCH_3), 2.32 (s, 3 H, $ArCH_3$), 4.03 (s, 3 H, OCH_3), 5.98 (q, J = 7 Hz, 1 H, $\underline{CH}CH_3$), 6.39 (d, J = 16 Hz, 1 H, COCH=), 7.00 (d, J = 16 Hz, 1 H, COCH=CH), 7.33 (d, J = 8 Hz, 1 H, ArH), 7.60 (s, 1 H, ArH), 7.70 (t, J = 8 Hz, 1 H, ArH), 7.94 (d, J = 8 Hz, 1 H, ArH), 13.02 (s, 1 H, ArOH); MS m/e 376 ($M^{+\cdot}$), 295, 281.

Method B: To a solution of 34 (26 mg, 0.064 mmol) in tetrahydrofuran (10 mL) was added cupric bromide (31.3 mg, 0.14 mmol) and the reaction mixture was heated at reflux for 4 h. The cuprous bromide which formed was filtered and the filtrate was evaporated under reduced pressure to give a brown residue. Chromatographic separation (10 g, silica gel, CH_2Cl_2) of the residue furnished 10 mg (42%) of 35 identical with the sample obtained by method A.

Method C: The compound 35 was obtained in 13% yield as a by-product when O-hydroxy dienone 32 was heated at reflux in the presence of SeO_2 to furnish anthrapyrone 33 via dehydrocyclization.

2-Acetyl-1(2'-methyl-2'(E)-butenoyloxy)benzene (41); A mixture of O-hydroxy acetophenone (39) (1.16g, 8.53 mmol), tiglyoyl chloride (40), and pyridine (6 mL) was heated at reflux overnight. The resulting dark-brown solution was poured into cold 10% aqueous HCl (200 mL), then extracted with dichloromethane (2 x 150 mL). The combined dichloromethane extracts were washed with water and brine, then dried ($MgSO_4$), filtered, and evaporated to give a brown oil: ^1H NMR (CCl_4) δ 1.89 (d, J = 7 Hz, 3 H, $=CHCH_3$), 1.93 (s, 3 H, $C=CCH_3$), 2.42 (s, 3 H, $COCH_3$), 6.93 - 7.54 (m, 3 H, ArH), 7.62 (d'd, J = 7 and 2 Hz, 1 H, ArH).

1-Hydroxy-2-(4'-methyl-hexa-4'(E)-ene-1',3'-dionyl)benzene (42); A mixture of 41 (1.86 g, 8.55 mmol), dioxane (50 mL), and 50% NaH (1.00g, 21 mmol) was heated on a steam bath for 3 h. The resulting dark solution was cooled, then quenched with glacial acetic acid. The solvent was removed, and the residue was dissolved in ethyl acetate (200 mL). The solution was washed with water and brine, then dried ($MgSO_4$), filtered, and evaporated to furnish 42 as an oil: ^1H NMR (CCl_4) δ 1.88 (d, J = 7 Hz, 3 H, $=CHCH_3$), 2.55 (s, 3 H, $C=CCH_3$), 6.28 (s, 1 H, CH=COH), 6.68 - 6.98 (m, 2 H, ArH), 7.36 (t, J = 7 Hz, 1 H, ArH), 7.60 (d, J = 7 Hz, 1 H, ArH), 11.89 (s, 1 H, ArOH), 12.08 (s, 1 H, CH=COH); MS m/e 218 ($M^{+\cdot}$), 203, 263, 121.

2-(1'-methyl-1'(E)-propenyl)benzo[1,2-*b*]pyran-4-one (43); A mixture of 42 obtained above, glacial acetic acid (30 mL), and excess sodium acetate (3-4g) was heated on a steam bath for 7 h. The acetic acid was evaporated at reduced pressue to give an oil, which was dissolved in ethyl acetate (200 mL). The ethyl acetate extract was washed with water, aqueous $NaHCO_3$, and brine, then dried ($MgSO_4$), filtered, and evaporated to give a brown oil. Further purification was accomplished by column chromatography (100 g, silica gel, CH_2Cl_2 to 10% EtOAc-CH_2Cl_2) to furnish 0.95 g (75% overall yield from 36) of 43 as a colorless oil: ^{1}H NMR (CCl_4) δ 1.88 (d, J = 7 Hz, 3 H, =CHC$\underline{H}_3$), 1.90 (s, 3 H, =CCH_3), 6.14 (s, 1 H, C=CH), 6.64 (q, J=7 Hz, 1 H, =C$\underline{H}$CH_3), 7.16 - 7.66 (m, 3 H, ArH), 8.04 (d, J = 7 Hz, 1 H, ArH); MS m/e 200 ($M^{+\cdot}$), 185, 120.

2-Acetyl-3-methyl-1(2'-methyl-2'(E)-butenoyloxy)-8,9,10-trimethoxyanthracene (44); A mixture of 27 (140 mg, 0.41 mmol), excess tigloyl chloride (40) (350 mg, 3.38 mmol), and pyridine (10 mL) was stirred under N_2 at room temperature overnight. The reaction mixture was poured into cold aqueous 10% HCl (150 mL), then extracted with ethyl acetate (150 mL). The ethyl acetate solution was washed with water and brine, then dried ($MgSO_4$), filtered, and evaporated under reduced pressure to give a foam. The crude product was purified by column chromatography (75 g, silica gel, CH_2Cl_2 to 5% EtOAc-CH_2Cl_2) to furnish 170 mg (80%) of ester 44 as a brown solid. Recrystallization of the material from hexanes provided yellow needles: mp 161-163°C; ^{1}H NMR (CCl_4) δ 1.90 (d, J = 7 Hz, 3 H, =CHC$\underline{H}_3$), 1.99 (s, 3 H, =CCH_3), 2.30 (s, 6 H, ArCH_3 and COCH_3), 3.64 (s, 3 H, OCH_3), 3.84

(s, 3 H, OCH_3), 3.94 (s, 3 H, OCH_3), 6.56 (d, J = 7 Hz, 1 H, ArH), 7.08 (q, J = 7 Hz, 1 H, $=C\underline{H}CH_3$), 7.15 (t, J = 8 Hz, 1 H, ArH), 7.68 (d, J = 8 Hz, 1 H, ArH), 7.83 (s, 1 H, ArH); MS m/e 422 ($M^{+\cdot}$), 407, 340, 325.

2-Acetyl-3-methyl-1,8,9,10-tetramethoxyanthracene (46); A stirred mixture of 27 (200 mg, 0.59 mmol), dimethyl sulfate (96.3 mg, 0.76 mmol), and anhydrous potassium carbonate (162 mg, 1.18 mmol) in acetone (25 mL) was heated at reflux overnight. The initial brown mixture became lighter during this period. After cooling the reaction mixture, inorganic material was removed by filtration. The filtrate was evaporated to give an oil which was dissolved in ether (100 mL) and treated with triethylamine (1 mL). After standing for 1 h, the ether solution was washed with water, 10% HCl and brine, then dried ($MgSO_4$), filtered, and evaporated to furnish an oil. Column chromatography (30 g, silica gel, CH_2Cl_2) of the oil afforded 190 mg (91%) of permethylated anthracene 46 as a yellow solid: mp 124-126°C; ^1H NMR (CCl_4) δ 2.40 (s, 3 H, $ArCH_3$), 2.56 (s, 3 H, $COCH_3$), 3.86 (s, 3 H, OCH_3), 3.99 (s, 3 H, OCH_3), 6.66 (d, J = 7 Hz, 1 H, ArH), 7.25 (t, J = 7 Hz, 1 H, ArH), 7.73 (d, J = 7 Hz, 1 H, ArH), 7.75 (s, 1 H, ArH).

2-Acetyl-8-methoxy-3-methyl-1(2'-methyl-2'(E)-butenoyloxy anthraquinone (48); To a solution of 44 (160 mg, 0.38 mmol) in THF (30 mL) was added cupric bromide (223 mg, 0.76 mmol) and the mixture was heated at reflux for 3.5 h. The inorganic material was removed by filtration and the filtrate was evaporated to dryness. The resulting residue was dissolved in ethyl acetate (50 mL), washed with water and brine, then dried ($NaSO_4$), filtered and evaporated to give

a brown solid, which was further purified by column chromatography (10 g, silica gel, CH_2Cl_2 to 5% EtOAc-CH_2Cl_2) to furnish 114 mg (77%) of 48 of a yellow solid. Recrystallization of the product from benzene-petroleum ether (30-65°) or acetone-hexanes provided pure 48 as yellow plates: mp 179-181.5°C; ^{1}H NMR ($CDCl_3$) δ 1.97 (d, J = 7 Hz, 3 H, =CHC<u>H</u>$_3$), 2.06 (s, 3 H, CCH_3), 2.43 (s, 3 H, $ArCH_3$), 2.50 (s, 3 H, $COCH_3$), 3.96 (s, 3 H, OCH_3), 7.17 (q, J = 7 Hz, 1 H, C<u>H</u>CH_3), 7.30 (d, J = 7 Hz, 1 H, ArH), 7.64 (t, J = 7 Hz, 1 H, ArH), 7.87 (d, J = 7 Hz, 1 H,ArH), 8.01 (s, 1 H, ArH); MS m/e 392 ($M^{+\cdot}$), 348, 333, 310, 295.

<u>1-Hydroxy-8-Methoxy-3-methyl-2(4'-methyl-hexa-4'(E)-ene-1', 3'-dionyl) anthraquinone (49)</u>; To a stirred solution of 48 (43 mg, 0.11 mmol) in THF (3 mL) was added excess NaH(50%, 50 mg) and the resulting brown mixture was heated at reflux for 5 h. Tlc analysis of the reaction indicated that the starting material was consumed with formation of a single product, less polar than the starting ester. The reaction mixture was cooled to 0°C and quenched with glacial acetic acid. The organic material was extracted with ethyl acetate (100 mL), washed with water, and brine, then dried ($MgSO_4$), filtered and evaporated to furnish 40 mg (93%) of 49 as an orange solid. Since the material obtained appeared to undergo air oxidation, it was immediately used in the next reaction without further purification: ^{1}H NMR ($CDCl_3$) δ 1.89 (s, 3 H, $=CCH_3$), 1.91 (d, J = 7 Hz, 3 H, =CHC<u>H</u>$_3$), 2.47 (s, 3 H, $ArCH_3$), 4.06 (s, 3 H, OCH_3), 6.10 (s, 1 H, C<u>H</u>=COH), 6.87 (q, J = 7 Hz, 1 H, =C<u>H</u>CH_3), 7.36 (d, J = 7 Hz, 1 H, ArH), 7.60 (s, 1 H, ArH), 7.73 (t, J = 7 Hz, ArH), 7.89 (d, J = 7 Hz, 1 H, ArH), 12.89 (s, 1 H,

ArOH); MS m/e 392 ($M^{+\cdot}$), 377, 309, 295.

2-[6'-(2',3'-dihydro-(E)-2',3'-dimethyl)-4H-pyran-4-one]-1-hydroxy-8-methoxy-3-methylanthraquinone (51a) and Z-isomer (51b);

To a suspension of β-diketone 49 (37 mg, 0.094 mmol) in glacial acetic acid (2 mL) was added sodium acetate (200 mg, 2.4 mmol). The mixture was then heated overnight on an oil bath at 100-115°C. Tlc analysis of the reaction mixture indicated that two new products had formed and that the starting material was consumed. The resulting yellow reaction mixture was cooled to room temperature, then diluted with ethyl acetate (50 mL). The ethyl acetate solution was washed with water and brine, then dried ($MgSO_4$), filtered and evaporated under reduced pressure to give an orange residue. Chromatographic separation (75 g, silica gel, CH_2Cl_2) of the crude product furnished 28 mg (75%) of 51a and 8 mg (22%) of 51b both as orange solids. Recrystallization of the materials from acetone-hexanes provided pure samples: 51a: mp 228-230°C; ^1H NMR ($CDCl_3$) δ 1.22 (d, J = 7 Hz, 3 H, $OCHC\underline{H}_3$), 1.55 (d, J = 7 Hz, 3 H, $COCHC\underline{H}_3$), 2.43 (s, 3 H, $ArCH_3$),2.53 (d't, J = 12 and 6 Hz, 1 H, $OC\underline{H}CH_3$), 4.04 (s, 3 H, OCH_3), 4.44 (d't, J = 12 and 6 Hz, 1 H, $CO\underline{CH}CH_3$), 5.59 (s, 1 H, C=CHCO), 7.34 (d, J = 8 Hz, 1 H, ArH), 7.59 (s, 1 H, ArH), 7.70 (t, J = 8 Hz, 1 H, ArH), 7.92 (d, J = 8 Hz, 1 H, ArH), 13.28 (s, 1 H, ArOH); MS m/e 392 ($M^{+\cdot}$); 51b: mp 194-196°C; ^1H NMR ($CDCl_3$) δ 1.27 (d, J = 7 Hz, 3 H, $OCHC\underline{H}_3$), 1.49 (d, J = 7 Hz, 3 H, $COCHC\underline{H}_3$), 2.46 (s, 3 H, $ArCH_3$), 2.50 (d't, J = 3.4 and 6 Hz, 1 H, $OC\underline{H}CH_3$), 4.07 (s, 3 H, OCH_3), 4.84 (d't, J = 3.4 and 6 Hz, 1 H, $CO\underline{CH}CH_3$), 5.54 (s, 1 H, C=CHCO), 7.34 (d, J = 8 Hz, 1 H, ArH), 7.62 (s, 1 H, ArH), 7.74 (t, J = 8 Hz, 1 H, ArH), 7.96 (d, J = 8 Hz, 1 H, ArH), 13.28 (s, 1 H, ArH); MS m/e 392 ($M^{+\cdot}$).

2-Acetyl-1,8-dimethoxy-3-methylanthraquinone(59); To a heated mixture of ethyl acetate-chloroform (1:1, 10 mL) and cupric bromide (54 mg, 0.24 mmol) was added a solution of permethylated anthracene 46 (40 mg, 0.11 mmol) in chloroform (5 mL). The reaction mixture was heated at reflux for 1 h, during which time the solution became dark and cuprous bromide precipitated. The inorganic material was removed by filtration and the filtrate was decolorized (charcoal), then evaporated under reduced pressure to give a brown residue. Purification of the product by column chromatography (10 g, silica gel, CH_2Cl_2) provided 31 mg (85%) of anthraquinone 59 as a solid. Recrystallization of the solid from methanol furnished pure 59 as yellow needles: mp 185-187°; ^1H NMR ($CDCl_3$) δ 2.37 (s, 3 H, $ArCH_3$), 2.56 (s, 3 H, $COCH_3$), 3.95 (s, 3 H, OCH_3), 4.03 (s, 3 H, OCH_3), 7.33 (d, J = 8 Hz, 1 H, ArH), 7.66 (t, J = 8 Hz, 1 H, ArH), 7.87 (d, J = 8 Hz, 1 H, ArH), 7.88 (s, 1 H, ArH); MS m/e 324 ($M^{+\cdot}$), 309.

1-Hydroxy-3-methyl-8,9,10-trimethoxyanthracene (60); To a stirred solution of sodium methoxide, prepared by dissolving sodium (20 mg, 0.87 mmol) in methanol (5 mL) at room temperature, was added a solution of 32 (40 mg, 0.87 mmol) in methanol (5 mL). The resulting deep-red solution was stirred at room temperature for 1 h at which time tlc analysis indicated that several new products had formed. A few drops of distilled water were added to the mixture and the mixture was then heated at reflux overnight. A second tlc analysis of the reaction mixture then indicated that a major product was produced. The reaction mixture was cooled, then quenched with glacial acetic acid. After removal of the methanol under reduced pressure, the residue was

dissolved in ethyl acetate (50 mL), which was washed with water and brine. The ethyl acetate solution was dried ($MgSO_4$),filtered and evaporated to give a pale-yellow solid. Chromatographic separation (20 g, silica gel, CH_2Cl_2 to 5% EtOAc-CH_2Cl_2) of the product furnished 16.2 mg (55%) of 60 as a yellow solid. Recrystallization of the material from acetone-petroleum ether(30-65°) provided pure 60 as yellow needles: mp 109-110°C; ^{1}H NMR (CCl_4) δ 2.49 (s, 3 H, $ArCH_3$), 3.93 (s, 3 H, OCH_3), 3.96 (s, 6 H, 2 OCH_3), 6.61 (d, J = 7 Hz, 1 H, ArH), 7.18 (t, J = 7 Hz, 1 H, ArH), 7.37 (s, 1 H, ArH), 7.72 (d, J = 8 Hz, 1 H, ArH), 9.92 (s, 1 H, ArOH); MS m/e 298 ($M^{+\cdot}$), 283, 268.

Methyl 1,4-dimethoxy-3-phenylthiomethyl-2-naphthoate (61); Compound 61 was prepared in a manner similar to that described for 25a. Thus, methyl 3-bromomethyl-1,4-dimethoxy-2-naphthoate [67] (3.00 g, 8.35 mmol) furnished 3.11 g (95%) of pure 61 as colorless needles after chromatographic separation, followed by recrystallization from acetone-hexanes or ether: mp 114-115°C; ^{1}H NMR ($CDCl_3$) δ 3.86 (s, 3 H, OCH_3), 3.94 (s, 3 H, OCH_3), 4.00 (s, 3 H, OCH_3), 4.50 (s, 2 H, ϕSCH_2), 7.16 - 7.62 (m, 7 H, ArH), 7.98 - 8.22 (m, 2 H, ArH).

Methyl 1,4-dimethoxy-3-phenylsulfinylmethyl-2-naphthoate (62); Compound 62 was prepared by methods A and B described for the preparation of 26a.

Method A: Compound 61 (1.5 g, 4.1 mmol) was converted to 1.4 g (89%) of sulfoxide 62 by stirring with aqueous $NaIO_4$ (3.13 g, 14.6 mmol) at room temperature for 4.5 days. The product was

recrystallized from benzene-petroleum ether (30-65°) to give colorless plates: mp 126-127°C; ^{1}H NMR ($CDCl_3$) δ 3.92 (s, 3 H, OCH_3), 3.97 (s, 3 H, OCH_3), 3.99 (s, 3 H, OCH_3), 4.32 (d, J = 13 Hz, 1 H, PhSOCH(H), 4.65 (d, J = 13 Hz, 1 H, PhSOCH(H)), 7.40 - 7.70 (m, 7 H, ArH), 7.97 - 8.23 (m, 2 H, ArH).

Method B: Compound 61 (0.5 g, 1.36 mmol) yielded 400 mg (77%) of sulfoxide 62 by oxidation with m-chloroperbenzoic acid (223.5 mg, 1.36 mmol) followed by chromatographic separation and recrystallization.

2-Acetyl-9,10-dimethoxy-1-hydroxy-3-methylanthracene (63); Preparation of 63 was accomplished in 54% yield using the procedure described for 27. The product was obtained as orange needles following recrystallization from benzene-petroleum ether (30-65°): mp 109 - 110°C; ^{1}H NMR (CCl_4) δ 2.44 (s, 3 H, $ArCH_3$), 2.59 (s, 3 H, $COCH_3$), 3.96 (s, 3 H, OCH_3), 4.03 (s, 3 H, OCH_3), 7.3 - 7.5 (m, 2 H, ArH), 7.40 (s, 1 H, ArH), 7.97 - 8.24 (m, 2 H, ArH), 11.53 (s, 1 H, ArOH); MS m/e 310 ($M^{+\cdot}$), 295, 281.

9,10-Dimethoxy-1-hydroxy-3-methyl-2(4'-methyl-hexa-2'(E), 4'(E)-dienoyl) anthracene (64); Compound 64 was prepared in 70% yield from 63 by the method described for the preparation of 32. Recrystallization of the product from benzene-petroleum ether (30-65°) provided 64 as a yellow powder: mp 122-124°C; ^{1}H NMR (CCl_4) δ 1.75 (d, J = 7 Hz, 3 H, CH_3CH), 1.80 (s, 3 H, CCH_3), 2.41 (s, 3 H, $ArCH_3$), 3.98 (s, 3 H, OCH_3), 4.05 (s, 3 H, OCH_3), 5.86 (q, J = 7 Hz, 1 H, CH_3CH), 6.48

(d, J = 16 Hz, 1 H, COCH=), 7.06 (d, J = 16 Hz, 1 H, COCH=CH), 7.2 - 7.42 (m, 2 H, ArH), 7.47 (s, 1 H, ArH), 7.90 - 8.20 (m, 2 H, ArH), 10.64 (s, 1 H, ArOH); MS m/e 376 ($M^{+\cdot}$), 361, 295, 279.

7,12-Dimethoxy-5-methyl-2(1'-methyl-1'(E)-propenyl)-2,3-dihydro-4H-anthra[1,2-*b*]pyran-4-one(65); Preparation of 65 from 64 was accomplished in 61% yield using the procedure described for preparation of 34 (Method A). The product was isolated as an orange-brown powder which was recrystallized from benzene-petroleum ether (30-65°): mp 153-155°C; ^{1}H NMR ($CDCl_3$) δ 1.76 (d, J = 7 Hz, 3 H, =CHCH_3), 1.94 (s, 3 H, =CCH_3), 2.68 (d'd, J = 16 and 4 Hz, 1 H, $COCH_e$), 3.10 (d'd, J = 16 and 14 Hz, 1 H, $COCH_a$), 3.96 (s, 3 H, OCH_3), 4.06 (s, 3 H, OCH_3), 5.00 (d'd, J = 14 and 4 Hz, OCH), 5.82 (q, J = 7 Hz, 1 H, =CHCH_3), 7.40 - 7.60 (m, 3 H, ArH), 8.10 - 8.42 (m, 2 H, ArH); MS m/e 376 ($M^{+\cdot}$), 361, 294.

7,12-Dimethoxy-5-methyl-2(1'-methyl-1'(E)-propenyl)-3-bromo-2-hydro-4H-anthra[1,2-*b*]pyran-4-one(66);

Method A: To a solution of 65 (3.6 mg, 0.096 mmol) in THF (10 mL) was added cupric bromide (47 mg, 0.23 mmol) and the mixture was heated at reflux for 3 h. The cuprous bromide which formed was removed by filtration and the filtrate was evaporated to dryness under reduced pressure. The resulting brown residue was purified by column chromatography (25, silica gel, C_6H_6) to give 17 mg (39%) of 66 as an orange solid, which was recrystallized from benzene-petroleum ether to provide pure 66 as orange crystals: mp 167-170°C; ^{1}H NMR (CCl_4)

δ 1.75 (d, J = 7 Hz, 1 H, =CHC<u>H</u>$_3$), 1.87 (s, 3 H, =CC<u>H</u>$_3$), 2.72 (s, 3 H, ArC<u>H</u>$_3$), 3.92 (s, 3 H, OC<u>H</u>$_3$), 4.00 (s, 3 H, OC<u>H</u>$_3$), 4.78 (d, J = 9 Hz, 1 H, COCHBr), 5.03 (d, J = 9 Hz, 1 H, C<u>H</u>CHBr, 5.69 (q, J = 7 Hz, 1 H, =C<u>H</u>CH$_3$), 7.34 - 7.58 (m, 3 H, ArH), 8.04 - 8.30 (m, 2 H, ArH); MS m/e 454 ($M^{+\cdot}$), 439, 374, 359.

<u>Method B</u>: To a stirred solution of <u>65</u> (33.5 mg, 0.089 mmol) in THF (7 mL), cooled to -78°C, was added phenyltrimethylammoniumperbromide (PTAB) (34 mg, 0.090 mmol) and the reaction mixture was slowly brought to room temperature. Tlc analysis of the reaction after stirring at room temperature overnight indicated that a substantial amount of unreacted starting material remained. An additional 30 mg of PTAB was added to the reaction mixture and stirring was continued at room temperature for 8 h. The reaction mixture was poured into a cold 1:1 mixture of saturated $NaHCO_3$ and $Na_2S_2O_3$ solution (50 mL) and extracted with ethyl acetate (2 x 50 mL). The ethyl acetate extracts were combined, washed with water and brine, then dried ($MgSO_4$), filtered and evaporated under reduced pressure to give a brown residue. The residue was purified by column chromatography (10g, silica gel, C_6H_6-CH_2Cl_2(50:50)) to furnish 18 mg (44%) of bromo compound <u>66</u>. The sample obtained was identical with the material prepared by Method A.

<u>7,12-Dimethoxy-5-methyl-2(1'-methyl-1'(E)-propenyl)-4H-anthra[1,2-*b*]pyran-4-one(67)</u>;

<u>Method A</u>: To a solution of bromo ketone <u>66</u> (17 mg, 0.037 mmol) in tetrahydrofuran (THF) (5 mL), cooled to 0°C, was added

1,5-diazabicycloundec-5-ene(DBU) (9.12 mg, 0.06 mmol) and the mixture was stirred at 0°C for 3 h. After removal of the solvent under reduced pressure, the resulting residue was dissolved in ethyl acetate (50 mL), which was washed with water and brine. The organic solution was dried ($MgSO_4$), filtered, and evaporated to give a brown residue, which was purified by column chromatography (10 g, silica gel, 3% EtOAc-CH_2Cl_2) to furnish 9 mg (64%) of dimethoxy anthrapyran 67 as a yellow solid. Recrystallization of the product from benzene-petroleum ether (30-65°) provided a pure sample: mp 145-147°C; ^1H NMR (CCl_4) δ 1.98 (d, J = 7 Hz, 3 H, =CH$\underline{CH_3}$), 2.01 (s, 3 H, =C$\underline{CH_3}$), 2.88 (s, 3 H, ArCH_3), 3.90 (s, 3 H, OCH_3), 4.03 (s, 3 H, OCH_3), 6.24 (s, 1 H, CO=CH), 7.20 (q, J = 7 Hz, 1 H, =$\underline{CH}CH_3$), 7.36 - 7.58 (m, 2 H, ArH), 7.69 (s, 1 H, ArH), 8.10 - 8.40 (m, 2 H, ArH); MS m/e 374 ($M^{+\cdot}$), 359, 279, 265.

Method B: A mixture of 65 (38.7 mg, 0.103 mmol) and 2,3-dichloro-5 , 6-dicyanobenzoquinone (51.7mg, 0.23 mmol) in benzene (10 mL) was heated at reflux for 40 h. The resulting dark solution was diluted with ethyl acetate (50 mL), and washed with water and brine. The ethyl acetate solution was dried ($MgSO_4$), filtered and evaporated to give a brown residue. Purification by column chromatography (10 g, silica gel, CH_2Cl_2) furnished 3 mg (8.4%) of 67, identical with the sample prepared by method A and 4.8 mg (13%) of 5-methyl-2(1'-methyl-1'(E)-propenyl)-2,3-dihydro-4H-anthra[1,2-*b*]pyran-4,7,12-trione (68). Compound 68 was recrystallized from benzene-petroleum ether (30-65°) to give brown-red crystals: mp 216-219°C; ^1H NMR ($CDCl_3$) δ 1.75 (d, J = 7 Hz, 3 H, =CH$\underline{CH_3}$), 1.90 (s, 3 H, =CCH_3), 2.80

(s, 3 H, $ArCH_3$), 2.90 (m, 2 H, $COCH_2$), 4.90 (d'd, J = 14 and 4 Hz, 1 H, OCH), 5.88 (q, J = 7 Hz, 1 H, $=C\underline{H}CH_3$), 7.60 - 7.85 (m, 2 H, ArH), 7.76 (s, 1 H, ArH), 8.15 - 8.40 (m, 2 H, ArH); MS m/e 346 ($M^{+\cdot}$), 331, 264.

11-Methoxy-5-methyl-2(1'-methyl-1'(E)-propenyl)-2,3-dihydro-4H-anthra[1,2-*b*]pyran-4,7,12-trione(69); A mixture of 34 (100 mg, 0.25 mmol) and DDQ (83.5 mg, 0.37 mmol) in tetrahydrofuran (20 mL) was heated at reflux overnight. The solid generated in the reaction was removed by filtration through a celite pad and the filtrate was evaporated under reduced pressue to give a brown residue. Chromatographic separation (35 g, silica gel, CH_2Cl_2 to 10% EtOAc-CH_2Cl_2) of the residue furnished 38.3 mg (41%) of anthraquinone 69 as a yellow powder. Recrystallization of the material from dichloromethane-hexanes provided a pure sample of 69: mp 203-205°C; ^1H NMR ($CDCl_3$) δ 1.71 (d, J = 7 Hz, 3 H, $=CH\underline{CH_3}$), 1.86 (s, 3 H, $=CCH_3$), 2.71 (s, 3 H, $ArCH_3$), 2.60 - 3.20 (m, 2 H, $COCH_2$), 3.99 (s, 3 H, OCH_3), 4.96 (d'd, J = 12 and 5 Hz, 1 H, $O\underline{CH}CH_2$), 5.80 (q, J = 6 Hz, 1 H, $=C\underline{H}CH_3$), 7.30 (d, J = 8 Hz, 1 H, ArH), 7.59 (s, 1 H, ArH), 7.60 (t, J = 8 Hz, 1 H, ArH), 7.81 (d, J = 8 Hz, 1 H, ArH); MS m/e 376 ($M^{+\cdot}$), 361, 294.

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78. Preparation of this compound is described in page 76.

79. Methyl 4,6-dimethoxy-2-phenylthiomethylbenzoate, an oil, was prepared in 80% yield by reacting the anion of methyl 4,6-dimethoxy-2-methylbenzoate, generated with 1 equivalent of lithium diisopropylamide at -78°C, with 1 equivalent of diphenyl disulfide. Methyl 4,6-dimethoxy-2-methylbenzoate was prepared in quantitative yield from dimethyl orsellinic acid[32] by esterification with diazomethane.

VITA

The author, Richard Poongnai Rhee, was born in Namwon, South Korea on March 30, 1942. He attended Taejon College (now Sungjun University) in Taejon, Korea and earned the degree Bachelor of Science in chemistry in 1965. Following graduation from the college, he joined the Korean army and spent the next three years in the Chemical, Biological and Radiological Warfare Division. In 1968, he came to the United States of America for further study and attended California State University, Fresno, California from 1970 to 1973. After earning an M.S. degree in organic chemistry under Dr. W. R. Biggerstaff, he moved to Corvallis, Oregon where he began graduate study in chemistry under Dr. J. D. White. During his two year stay at O.S.U. he was naturalized and became a U.S. citizen. In 1975, he moved to Portland, Oregon and joined the Oregon Graduate Center in Beaverton, Oregon to work as a research assistant under Dr. Frank M. Hauser in the Department of Chemistry. In 1977, he became a graduate student at the Oregon Graduate Center and continued his doctoral studies.

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