SYNTHETIC STUDIES OF NATURALLY OCCURRING HYDROXYLATED POLYCYCLIC COMPOUNDS: DAUNOMYCINONE AND PILLAROMYCINONE

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The dissertation "Synthetic Studies of Naturally Occurring Hydroxylated Polycyclic Compounds: Daunomycinone and Pillaromycinone" by Vaceli M. Baghdanov has been examined and approved by the following Examination Committee:

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Dedication

To my wife, Kathy.

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Abstract

Syntheses of daunomycinone and 11-deoxydaunomycinone from a common intermediate were established. In performing this task, a new synthesis of 6-acetyl-4a,5,6,7,8,8a-hexahydro-1(4H)-naphthalenone (I) from (*l*)-perilaldehyde was developed. Grignard condensation of allylmagnesium bromide with (*l*)-perilaldehyde gave an alcohol intermediate which was then treated with potassium hydride to effect oxy-Cope rearrangement to 2-(2-propenyl)-4-(1-methylethenyl)-cyclohexanecarboxaldehyde (II). The aldehyde intermediate was converted to 1-acetyl-4-(1-methylethenyl)-2-(2-propenyl)cyclohexane (III) by reaction of (II) with methyl lithium followed by Swern oxidation of the resultant alcohol. Ozonolysis of III furnished a diacetyl aldehyde intermediate which was cyclized with hydrogen chloride to give I.

9-Acetyl-5,12-dihydroxy-4-methoxy-7,8,9,10,10a,11-hexahydro-6(6aH)-naphthacenone (IV), which served as a common intermediate for daunomycinone and 11-deoxydaunomycinone, was prepared through condensation of 3-phenylsulfonyl-7-methoxy-1(3H)-isobenzofuranone with I. Regiospecific bromination of IV at the C-11 position with N-bromosuccinimide was followed by hydrolysis of the bromide to the C-11 alcohol product. Subsequent oxidation of the alcohol intermediate gave 9-acetyl-4,5,12-trimethoxy-6a,7,8,9,10,10a-hexahydronaphthacene-6,11-dione (V). Selenium dioxide dehydrogenation of V gave 9-acetyl-

4,5,12-trimethoxy-7,8,9,10-tetrahydronaphthacene-6,11-dione. Regiospecific demethylation of the C-5 and C-12 methyl ethers furnished 7,9-dideoxydaunomycinone.

Several approaches to pillaromycinone were examined. Michael condensation of ethyl 2-phenysulfinylmethylbenzoate (**VI**) with methyl 4-(2-cyclopentenyl)-3-butenoate yielded methyl 3-(2-cyclopentenylmethyl)-1-hydroxy-8-methoxynaphthalene-2-carboxylate (**VII**). Methylation of the phenolic group in **VII** and conversion of the methyl ester functionality to an aldehyde furnished 3-(2-cyclopentenylmethyl)-1,8-dimethoxynapthalene-2-carboxaldehyde (**VIII**). A variety of Lewis acids were examined in an attempt to catalyze intramolecular ene reaction between the aldehyde and cyclopentene functionalities in **VIII** to form 5,6-dimethoxy-11,11a-dihydro-(1H)-cyclopenta[b]anthracene.

Michael condensation of **VI** with methyl 4-(3-oxocyclopentyl)-3-butenoate ethylene acetal and then methylation of the phenolic group furnished methyl 1,8-dimethoxy-3-(3-oxocyclopentylmethyl)naphthalene-2-carboxylate ethylene acetal (**IX**). Sequential conversion of the ester funtionality in **IX** to an aldehyde, hydrolysis of the ketal group, and then intramolecular aldol cyclization gave 5,6-dimethoxy-2,3,11,11a-tetrahydro-3(1H)-cyclopenta[*b*]anthracenone (**X**). Reduction of the ketone in **X** to an alcohol was required prior to *cis*-hydroxylation of the double bond. After hydroxylation, oxidation of the alcohol back to the ketone yielded 3a,4-dihydroxy-5,6-dimethoxy-2,3,3a,4,11,11a-hexahydro-3(1H)-cyclopenta[*b*]anthracenone which was protected as the acetonide.

An efficient general method for the synthesis of 1(H)-2-benzopyran-1-ones was also developed. Condensation of *ortho*-carboxybenzaldehydes with various nitroalkanes furnished 3-nitroalkyl substituted 1(3H)-*iso*-benzofuranones. Reductive cleavage of the lactone functionality and Nef conversion of the nitro group to a carbonyl group gave *ortho*-carboxy-benzyl ketones. These were cyclodehydrated to 1(H)-2-benzopyran-1-ones with methyl, ethyl, phenyl, and *meta*-methoxyphenyl substituents at the C-3 position.

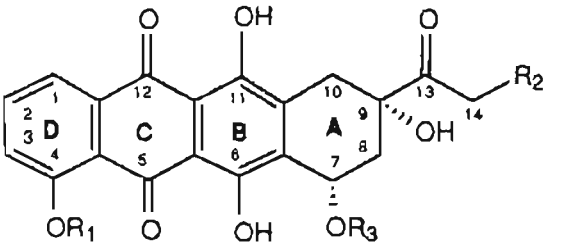
Part I: DAUNOMYCINONE

I. Introduction

A. Description

The considerable attention that has been given to the anthracyclines is due to their significant anticancer activity. Of the structurally diverse anthracyclines that have been discovered, daunorubicin and adriamycin continue to receive the greatest attention. For over twenty years, they have been used for the treatment of a variety of neoplastic diseases.

Anthracyclines are characterized by a linear polyhydroxylated tetracyclic aromatic ring system containing an anthraquinone chromophore. Subgrouping of anthracyclines is based upon the degree and pattern of hydroxylation. Although the most well known anthracyclines are daunorubicin (**1d**), adriamycin (**1e**), and carminomycin (**1f**), (Figure 1.1), other anthracyclines have also attracted attention. These include the rhodomycins, aclacinomycins, pyrromycins and nogalomycin.[1]



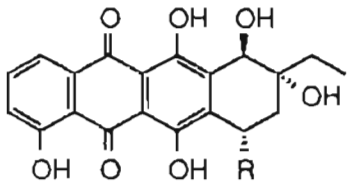
		R_1	R_2	R_3*
1a:	Daunomycinone	Me	H	H
1b:	Adriamycinone	Me	OH	H
1c:	Carminomycinone	H	H	H
1d:	Daunorubicin	Me	H	Daunosamine*
1e:	Adriamycin	Me	OH	Daunosamine*
1f:	Carminomycin	H	H	Daunosamine*

* See page 9 for the structures of the Sugar Substituents

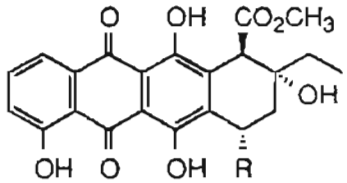
Figure 1.1 Daunomycinone series

B. Discovery and Isolation

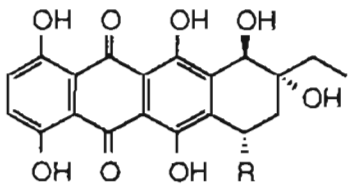
The first anthracyclines were discovered by Krassilnikov and Koreniakov in 1939.[2] No further studies were reported on their isolation, characterization, or chemistry until the 1950's when Brockmann and co-workers described the isolation of rhodomycins and isorhodomycins (Figure 1.2) from *Streptomyces purpurascens*.[3a] The aglycone of the rhodomycins consists of a 4,6,7,9,10,11-hexahydroxy-7,8,9,10-tetrahydro-5,12-naphthacenedione. The isorhodomycinones possess an additional hydroxyl group at C-1, and the ε-rhodomycinones and isorhodomycinones have a carbomethoxy group at C-10 rather than a hydroxyl.



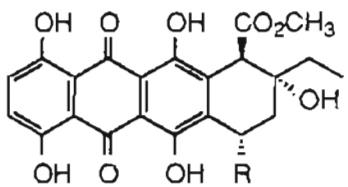
2a: β- Rhodomycinone R = OH
2b: γ- Rhodomycinone R = H
2c: Rhodomycin A R = Glycoside



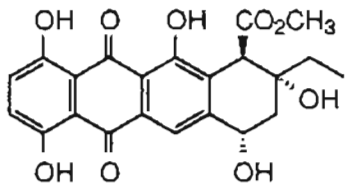
2d: ε- Rhodomycinone R = OH
2e: ζ- Rhodomycinone R = H
2f: Rhodomycin B R = Glycoside



2g: β- Isorhodomycinone R = OH
2h: γ- Isorhodomycinone R = H
2i: Isorhodomycin A R = Glycoside



2j: ε-Isorhodomycinone R = OH
2k: ζ-Isorhodomycinone R = H

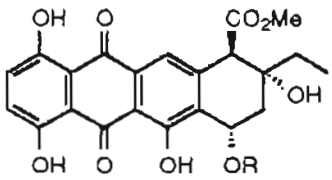


2l: δ-Rhodomycinone

Figure 1.2 Rhodomycinone series

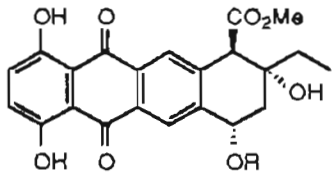
In 1957 Brockmann and co-workers reported the isolation of pyrromycin (**3b**, Figure 1.3) and its hydrolysis into ε-pyrromycinone (**3a**), and rhodosamine (**8a**, Figure 1.8).[3b,c] The pyrromycinones are characterized by a 1,4,6,7,9-pentahydroxy structure with a carbomethoxy functionality at C-10 and an ethyl group at C-9. Ettlinger and co-workers[4] isolated cinerubins A and B (**3c,d**) in 1959. The structures of the cinerubins were determined by Keller-Schierlein[5] and Richle[6] in 1970 and 1972 and shown to consist of a ε-pyrromycinone aglycone linked to trisaccharides. A variety of other anthracyclines were also discovered. Mitscher and co-workers at Lederle Laboratories isolated ruticulomycins A and B (**3l,m**) in 1964 from *Streptomyces rubrireticuli*.[7] The aglycone of the ruticulomycins was found to be 6-deoxypyrromycinone. In 1977, Nettleton and co-workers isolated two new glycosides of ε-pyrromycinone, marcellomycin (**3e**) and musetamycin, (**3f**) from the bohemic acid complex.[8] More recently, these same workers have isolated and characterized rudolphomycin (**3g**), alcindoromycin (**3h**), collinemycin (**3n**) and mimimycin (**3o**).[9]

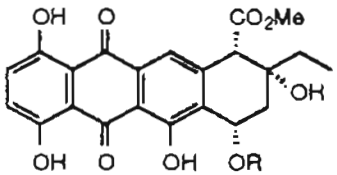
Bhuyan and co-workers at UpJohn isolated nogalomycin (Figure 1.4) from *Streptomyces nogalator* in 1965.[10] An unusual feature of this antibiotic is the presence of a sugar linked to the D ring by both a glycosidic linkage and a carbon-carbon bond.

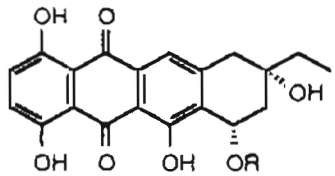


3a: ε-Pyrromycinone	R = H	3g: Rudolphomycin	R = Rhoa-O-Df-O-Red
3b: Pyrromycin	R = Rhoa	3h: Alcindoromycin	R = Mdr -O-Df-O-Df
3c: Cinerubin A	R = Rhoa-O-Df-O-Cin	3 i: Rhodirubin A	R = Rhoa-O-Df-O-Rho
3d: Cinerubin B	R = Rhoa-O-Df-O-Cin B	3 j: Rhodirubin B	R = Rhoa-O-Rho-O-Rho
3e: Marcellomycin	R = Rhoa-O-Df-O-Df	3k: Rhodirubin G	R = Rhoa -O-Df-O-D Cin
3 f: Mussetamycin	R = Rhoa-O Df		

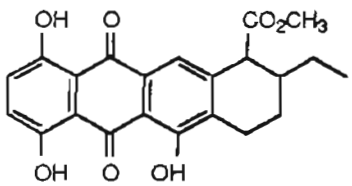
3 l: Ruticulomycin A	R = Unknown sugar
3m: Ruticulomycin B	R = Unknown sugar

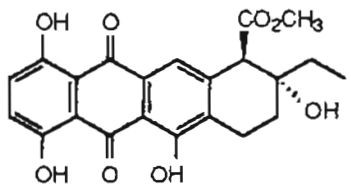






3n: Collinemycin	R = Rhoa-O-Df	3p: 10-Descarbomethoxy Marcellomycin	R = Rhoa-O-Df-O-Df
3o: Mimimycin	R = Rhoa-O-Df-O-Df	3q: 10-Descarbomethoxy Rudolphomycin	R = Rhoa-O-Df-O-Red

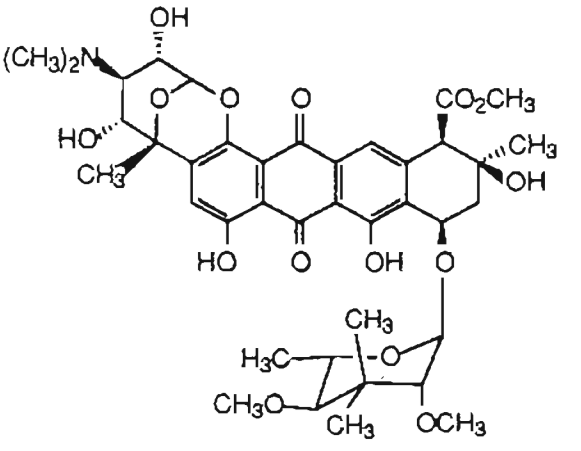




3r: η-Pyrromicinone

3s: ζ-Pyrromycinone

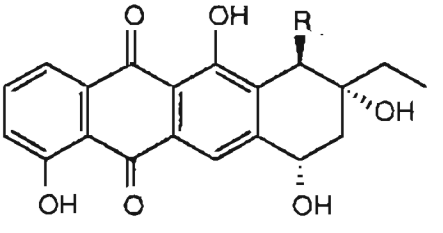
Figure 1.3 Pyrromycinone series



4: Nogalomycin

Figure 1.4

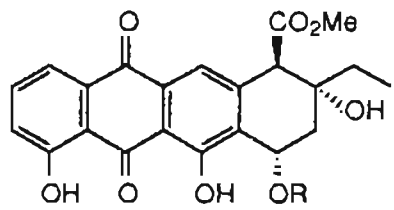
The rare citromycins were isolated by Brockmann in 1968 (Figure 1.5).[11] Their structures were proven by synthesis and shown to have either a 4,7,9,11-tetrahydroxy or a 4,7,9,10,11-pentahydroxy substitution pattern with an ethyl group at C-9.[12]



5a: α- Citromycinone R = OH
5b: γ- Citromycinone R = H

Figure 1.5

In 1956, Asheshov and co-workers described the isolation of aklavin (Figure 1.6) from an unidentified *Streptomyces* species collected at Aklavik, Canada.[13] The aglycone, aklavinone (**6a**), is characterized by a 4,6,7,9-tetrahydroxy structure with a carbomethoxy functionality at C-10 and an ethyl group at C-9. More recently (1975), Oki and co-workers isolated aclacinomycins A and B (**6c,d**) from *Streptomyces galilaeus*.[14] The aclacinomycins exhibit potent antitumor activity and are significantly less cardiotoxic than daunorubicin. Currently, these antibiotics are undergoing clinical trials.[15]



6a: Aklavinone	R = H
6b: Aklavin	R = Rhoa
6c: Aclacinomycin A	R = Rhoa-O-Df-O-Cin
6d: Aclacinomycin B	R = Rhoa-O-Df-O-Cin B

Figure 1.6 Aklavinone series

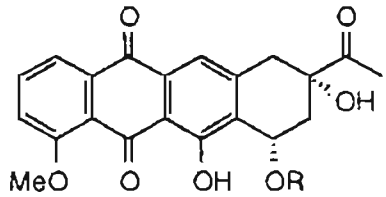
In 1963, two groups independently discovered daunorubicin. DiMarco and coworkers at Farmitalia accomplished their isolation from *Streptomyces peaucetius* and named the compound daunomycin, since the organism was obtained from a region of northern Italy, whose ancient name was Daunia.[16] The other group at Rhone-Polenc, headed by DuBost, performed their isolation from *Streptomyces coerubleorubidus* and named

it rubidomycin.[17] When the two compounds were shown to be identical, the name daunorubicin (**1d**) was chosen to reflect the dual origin (Figure 1.1). A series of spectroscopic and degradation studies of daunorubicin established its relative and absolute structure.[18] Daunorubicin was found to consist of the aglycone daunomycinone, which has a 4,6,7,9,11-pentahydroxy-9-acetyl substitution pattern, and the glycoside daunosamine (Figure 1.8). It was the first anthracycline to have clinical importance, especially in the treatment of leukemias.

In 1969, Arcamone and co-workers at Farmitalia, working with a different strain of *Streptomyces peucitius*, isolated the 14-hydroxy analog of daunorubicin which they named adriamycin (**1e**).[19] Adriamycin has proven to be an especially useful antitumor antibiotic. It is less toxic than daunorubicin, yet more active against a broader spectrum of tumors.

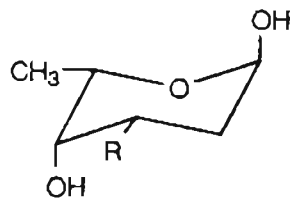
Gause and co-workers in the U.S.S.R. isolated the 4-demethyl analog of daunorubicin from *Actinomadura carminata* in 1973. This potent antitumor agent was named carminomycin (**1f**).[20]

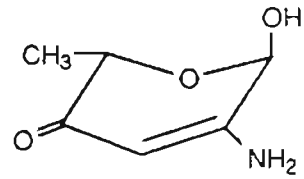
A new anthracycline, 11-deoxydaunorubicin was reported by Arcamone in 1980 (Figure 1.7).[21] It was obtained from *Micromonospora peucetica* and shown to be as active as daunorubicin, but less toxic.



7a: 11 - Deoxydaunorubicin R = Daunosamine
7b: 11 - Deoxydaunomycinone R = H

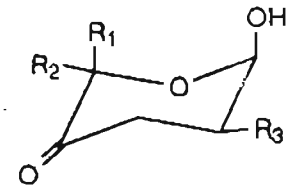
Figure 1.7





		R
8a: Rhoa	Rhodosamine	NMe_2
8b: Rho	Rhodinose	H
8c: Df	2-Deoxy-L-Fucose	OH
8d: Mdr	Monodemethylrhodosamine	NHMe
8e: Dau	Daunosamine	NH_2

8i: Red Rednose



		R_1	R_2	R_3
8f: Cin	L-Cinerulose	H	CH_3	H
8g: D Cin	D-Cinerulose	CH_3	H	H
8h: Cin B	Cinerulose B	H	CH_3	OH

Figure 1.8 Anthracycline Sugars

C. Clinical Studies

Initial biological and clinical studies of daunorubicin showed that it inhibited virus multiplication and was active against solid and ascite tumors. Like the previous anthracyclines, daunorubicin was cytotoxic; nevertheless, clinical studies were begun.[22] Daunorubicin was found to be the most active agent available for the treatment of acute non-lymphocytic leukemia and was also significantly active against acute lymphocytic leukemia. In addition, daunorubicin was useful for remission maintenance in acute leukemia and had useful activity against refractory or recurrent neuroblastoma.[23]

Adriamycin has the broadest spectrum of activity of any current anticancer drugs.[24] Adriamycin was active against cancers of the breast, bladder, lung, thyroid, ovary, osteogenic sarcoma, Wilm's tumor, neuroblastoma, Hodgkin's disease, and other lymphomas and leukemias and yet was less toxic than daunorubicin.

Carminomycin, the 4-demethyl analog of daunorubicin, though not as active as adriamycin, has relatively low cardiotoxicity and shows excellent potential for becoming a clinical agent.[25]

Preliminary evaluation of the 4-demethoxy analog of daunorubicin has established that it is equally or more active than daunorubicin against certain tumors and leukemias. Furthermore, it is less cardiotoxic and is orally active.[26] The 11-deoxy analog of daunorubicin (**7a**) had also been found to be as active but less cardiotoxic than daunorubicin.[21]

D. Biochemical Studies

Within a cell, daunorubicin was observed to alter the shape and size of the nucleolus and caused chromosomal damage during mitosis.[27] At high concentrations, mitosis was stopped and the chromosomes were scattered. The uptake of daunorubicin and its binding to DNA was found to be maximal during cell division.[28] These and other observations led DiMarco to suggest that daunorubicin binds to DNA by intercalation.[29] Initially it was proposed that the binding of daunorubicin to DNA caused strand breaks;[30] however, additional studies have shown that anthracyclines do not directly cause strand breaks, but rather induce conformational changes.[31] Upon intercalative binding, the DNA helix undergoes physiochemical changes such as elongation and stiffening. Although the consequences of the deformations in the intercalated DNA helix are not clearly established, it is assumed that the affinities of some DNA-dependent enzymes (polymerases, nucleases, ligases, ect.) are altered at the drug binding sites. Similarly, conformation-dependent changes in DNA structure, such as those that occur during phase transit of proliferating cells, may also be affected resulting in miotic blockage, chromosomal damage, and inhibition of DNA repair mechanisms.[32,33]

Comparison of the intercalative properties of anthracyclines , with other intercalating agents suggest that the toxicity of anthracyclines may not be simply attributed to its binding to DNA. This is baesed on the observation that though a large number of other agents have intercalating

properties, they lack the selective toxicity that anthracyclines posses. Nevertheless, DNA binding of the anthracyclines probably contributes to cytotoxicity and DNA damage. Furthermore, intercalative DNA binding may not be necessary or sufficient to account for the antitumor activity of anthracyclines. It has been hypothesized that anthracyclines with higher affinity for DNA are more protected from elimination and degradation than the more weakly bound agents. As the agent is slowly released from its protective site on the DNA, it may be metabolized into active forms and contribute to DNA damage.[34]

The fact that different anthracyclines possess different inhibition properties suggests that different mechanisms may be involved. Both daunorubicin and adriamycin inhibit both the RNA and DNA synthesis at similar concentrations; whereas, aclacinomycins inhibit RNA synthesis at a much lower concentration than that required for inhibition of DNA synthesis.[35] Furthermore, carminomycin and 11-0-methylcarminomycin exhibit potent antitumor activity, but are much less active than adriamycin in the inhibition of nucleic acid synthesis and both have markedly reduced DNA binding capacities.[36] These observations suggest that there are receptors other than the sites in DNA involved in drug activity, and that several different mechanisms may be involved.[37]

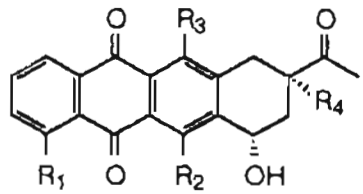
E. Analog and Structure-Activity Studies

In order to separate the toxicity and antitumor activities of these drugs, a number of structure-activity studies have been conducted. A variety of analogs have since been prepared to explore this objective.

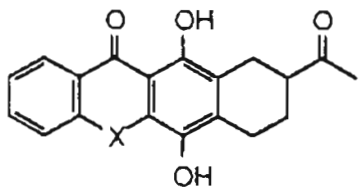
Since the activity of some anthracyclines has been shown to be dependent on the degree and pattern of hydroxyl substitution a variety of deoxy analogs have been prepared (Figure 1.9). The low cardiotoxicity and ease of synthesis of 4-demethoxydaunomycinone (**9a**) has led to numerous reports of its preparation.[38] There have also been syntheses of 4-demethoxy-11-deoxydaunomycinone (**9b**),[39] 6-deoxydaunomycinone (**9c**),[40] and 9-deoxydaunomycinone (**9d**).[41]

It has been suggested that the cardiotoxicity of anthracyclines arises from the redox chemistry of the quinone chromophore which generates radicals and superoxides, that then cause cellular damage. In order to alter the redox chemistry, the xantho analogs **10a** and **10b** have been prepared where one of the quinone carbonyl was replaced with an oxygen bridge.[42] Similarly, Wong has prepared the thioxantho analogs **10c** and **10d**.[43] In another variation, the carbonyls were replaced with nitrogen oxide bridges in **11**.[44]

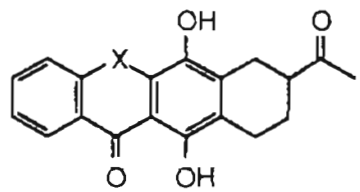
Hydrolytic cleavage of the glycoside to produce the aglycone, results in drug deactivation. In order to circumvent this problem, synthesis of a 7-thiodaunomycinone (**12**) was performed.[45]



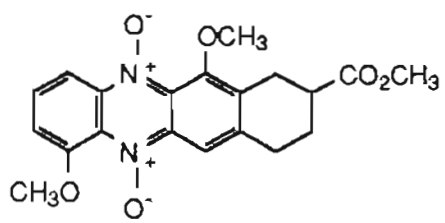
9a: $R_1 = H$ $R_2 = R_3 = R_4 = OH$
9b: $R_1 = R_3 = H$ $R_2 = R_4 = OH$
9c: $R_1 = CH_3O$ $R_2 = H$ $R_3 = R_4 = OH$
9d: $R_1 = CH_3O$ $R_2 = R_3 = OH$ $R_4 = H$



10a: X = O
10c: X = S



10b: X = O
10d: X = S



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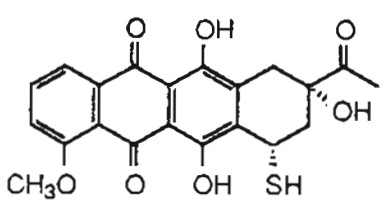


12

Figure 1.9. Analogs of Daunomycinone

II. Synthetic Background

The clinical importance of daunorubicin and adriamycin and the modest quantities that are produced by the fermentation processes (5-15 mg per liter of culture broth)[46] has stimulated efforts to develop efficient synthetic methodology applicable to the commercial production of daunomycinone and adriamycinone.

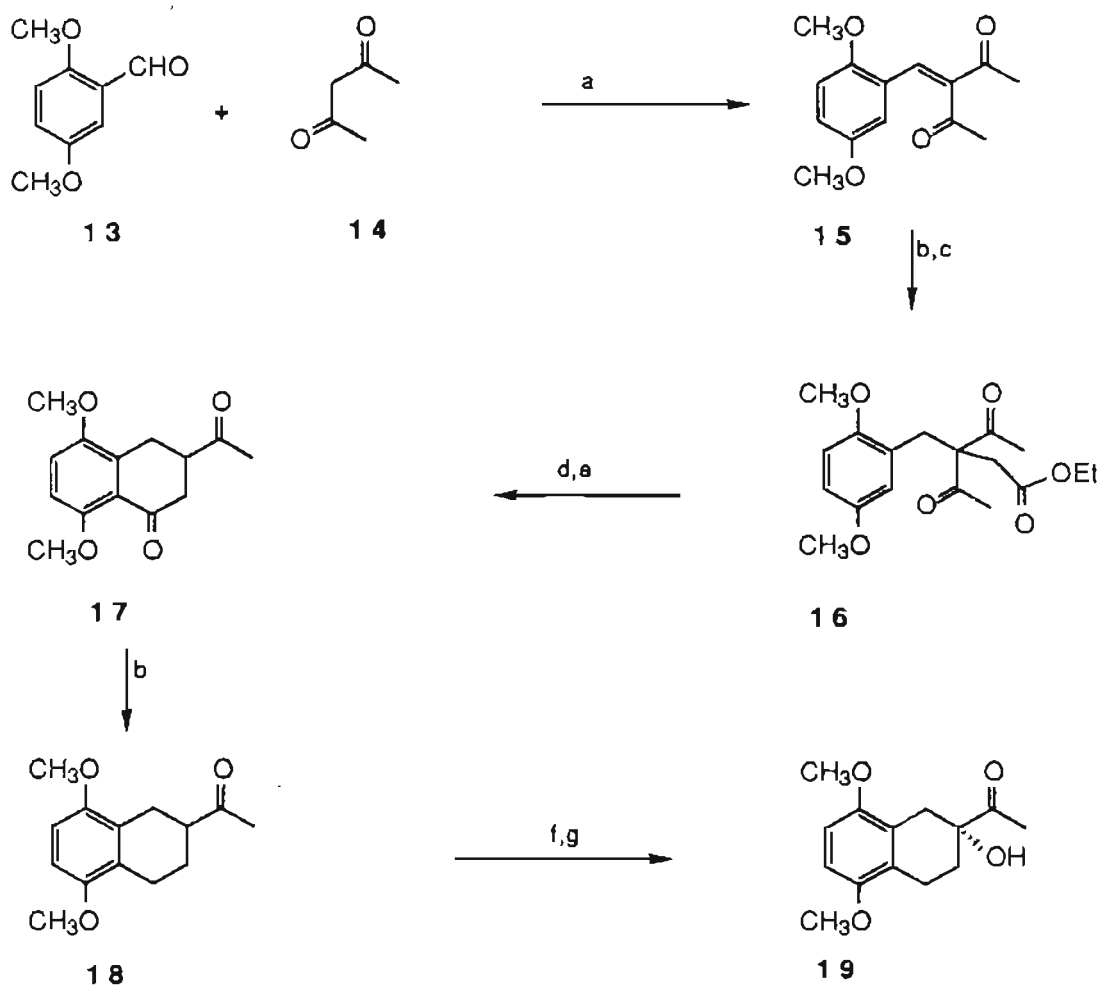
A. Non-Regiospecific Syntheses

The first total synthesis of racemic daunomycinone was reported by Wong in 1973 and is shown in Schemes 1.1 and 1.2.[47] The tetracyclic ring system was assembled utilizing Friedel-Craft acylation methodology developed by Goodman.[48]

The hydronaphthalene **19** was prepared from 2,5-dimethoxybenzaldehyde (**13**) as shown in Scheme 1.1. Knoevenagel condensation of **13** with 2,4-pentanedione (**14**) furnished the unsaturated diketone **15**. Sequential catalytic hydrogenation and then alkylation with ethyl bromoacetate gave the diketoester **16**. Treatment of **16** with sodium hydroxide effected cleavage of one of the acetyl groups and hydrolysis of the ester to the acid, which was subsequently cyclized to the tetralone **17**. Reductive removal of the ketone in **17** through hydrogenolysis gave **18**. The tertiary hydroxyl in **19** was introduced by reacting the enolate of **18**

with oxygen. The resultant hydroperoxy intermediate was reduced with zinc to furnish **19**.

Scheme 1.1 Wong's Synthesis

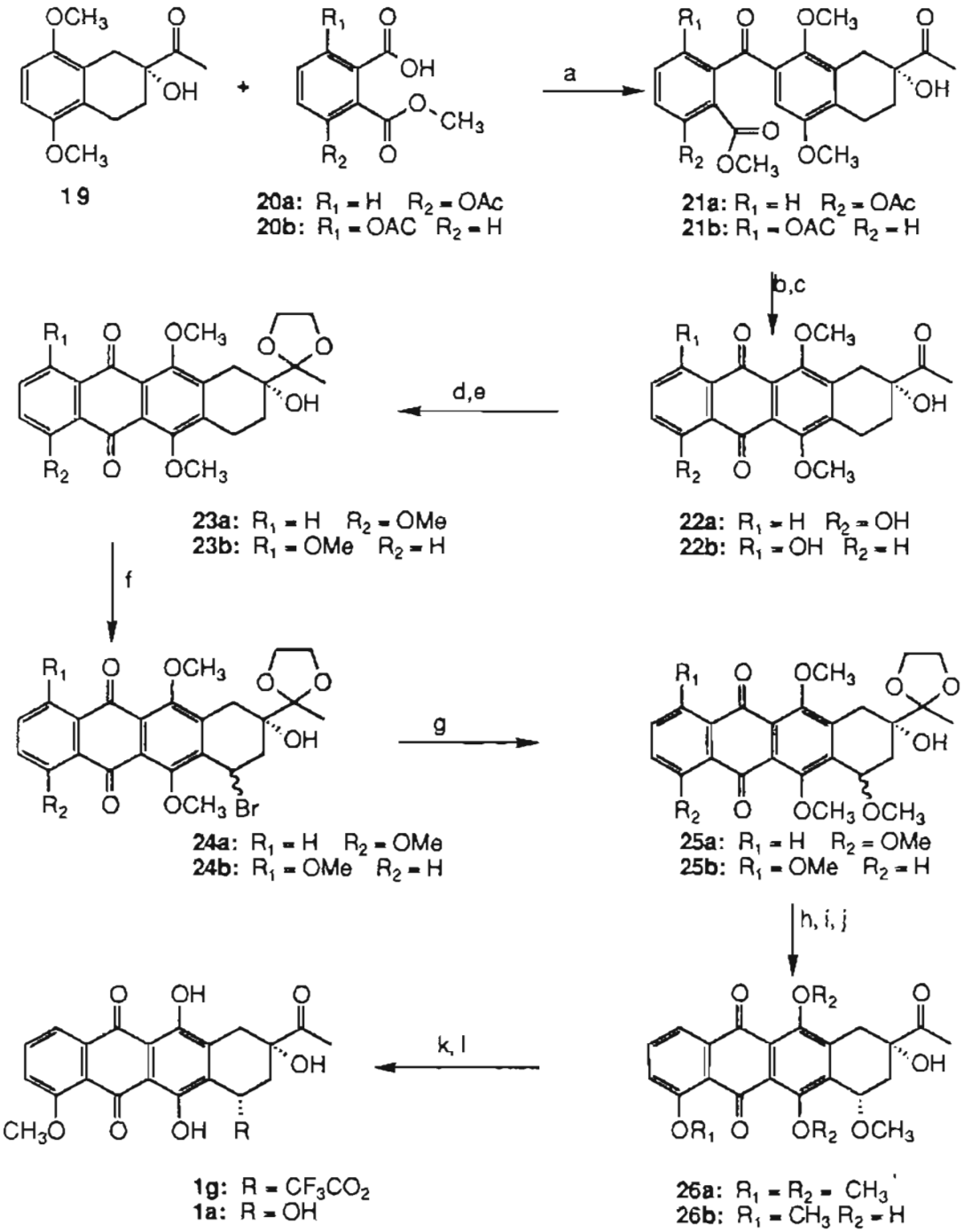


a. Piperidine, AcOH b. H_2, Pd-C c. NaH, $BrCH_2CO_2Et$
d. NaOH e. HF f. $KOBu^t$, O_2 g. Zn

Trifluoroacetic anhydride catalyzed condensation of the hydroxy ketone **19** with the isomeric mixture of 3-acetoxyphthalic acid mono-methyl esters (**20a,b**) yielded the diaryl ketones **21a** and **21b** (Scheme 1.2). The mixture was saponified and the acid product was subjected to intramolecular cyclization employing hydrogen fluoride. The product, an inseparable mixture of tetracyclic compounds **22a** and **22b**, was obtained in 19% overall yield. Methylation of the phenolic group in **22a,b** and protection of the ketone furnished the ketals **23a** and **23b**. Free radical bromination at C-7 with N-bromosuccinimide gave the isomeric bromides **24a** and **24b**. Methanolysis of the bromides **24a,b** furnished an epimeric mixture of C-7 methyl ethers **25a** and **25b**. Preparative thin layer chromatography yielded the α-epimer as a mixture of D ring isomers. Hydrolysis of the ketal group in the α epimers of **25a,b**, permitted the separation of the D ring isomers by preparative thin layer chromatography to furnish **26a**.

Demethylation of **26a** with aluminum chloride followed by oxidation with lead tetraacetate furnished an unstable diquinone intermediate, which was immediately remethylated on the D-ring to give, upon reduction, the quinone **26b** in 10% overall yield. Displacement of the benzylic C-7 methoxyl group with silver trifluoroacetate and hydrolysis of the resultant trifluoroacetate **1g** with ammonium hydroxide furnished daunomycinone (**1a**). The large number of isomers resulting from the lack of regioselectivity in annelating the tetracyclic system created considerable difficulty in the separation of isomers and contributed to a poor overall yield.

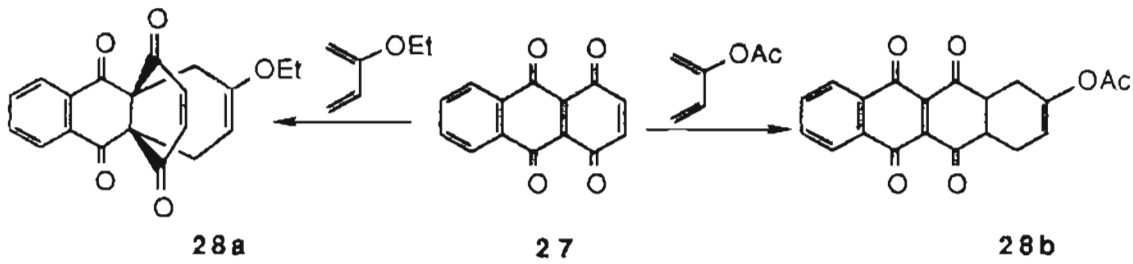
Scheme 1.2 Wong's Synthesis



a. TFAA b. NaOH c. HF d. Me_2SO_4, K_2CO_3
e. $HOCH_2CH_2OH$, H^+ f. NBS g. MeOH h. H^+
i. $AlCl_3$ j. $Pb(OAc)_4$ k. CF_3CO_2Ag l. NH_4OH

In a different approach, Kende, *et al.*, (1976) prepared racemic daunomycinone based on the Diels-Alder chemistry shown in Scheme 1.3.[49] This approach is based upon the differential reactivity of the bisquinone **27** with electron-rich and electron-poor dienes. For example, 2-acetoxybutadiene, an electron-poor diene, undergoes Diels-Alder reaction with the terminal double bond of the bisquinone **27** whereas, 2-ethoxybutadiene, an electron-rich diene, undergoes Diels-Alder reaction at the internal double bond.

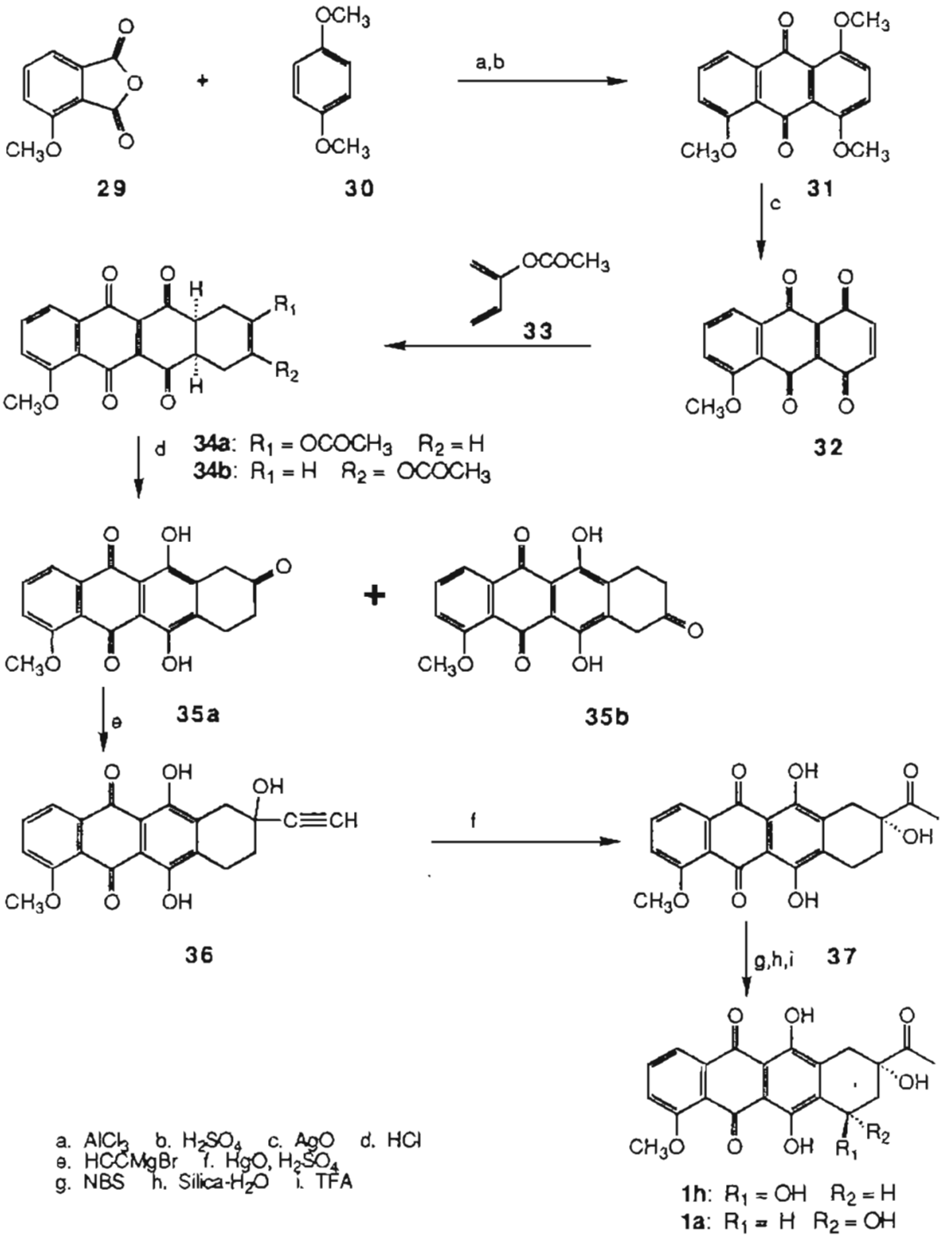
Scheme 1.3



Scheme 1.4 shows Kende's synthesis of daunomycinone. Regioselective Diels-Alder cycloaddition of 2-acetoxybutadiene with the terminal double bond of the diquinone **32** was exploited to construct the linearly fused tetracyclic adduct **34**.

Acylation of 1,4-dimethoxybenzene (**30**) with 3-methoxyphthalic anhydride (**29**) followed by intramolecular ring closure with sulfuric acid gave the dimethoxy quinone **31**. Oxidative demethylation of **31** with silver(II) oxide and nitric acid gave the diquinone **32** in 98% yield. Diels-Alder cycloaddition of **32** with 2-acetoxybutadiene (**33**) furnished the

Scheme 1.4 Kende's Diels-Alder Synthesis



adducts **34a** and **34b**) in 71% yield, as a 1:1 mixture of regioisomers. Acid hydrolysis of the enol acetate in **34a,b** was accompanied by aromatization of the B-ring to give **35a,b**. Pure **35a** was isolated by recrystallization from pyridine. Reaction of the ketone carbonyl in **35a** with excess ethynyl magnesium bromide furnished the ethynyl carbinol intermediate **36** in 52% yield. Mercuric ion catalyzed hydration of **36** gave 7-deoxydaunomycinone (**37**) in 40% yield. Free radical bromination of **37** gave the labile C-7 bromo compound which was hydrolyzed on moist silica gel to 7-*epi*-daunomycinone (**1h**) and daunomycinone (**1a**). Epimerization of **1h** with trifluoroacetic acid gave daunomycinone in 50% yield from **37**. Although this route is brief, straightforward, and can be done on a large scale, the lack of regioselectivity during the Diels-Alder addition and the inefficient conversion of the ketone **35a** to the hydroxy acetyl **37** significantly reduced the overall yield and efficiency.

B. Regiospecific Syntheses

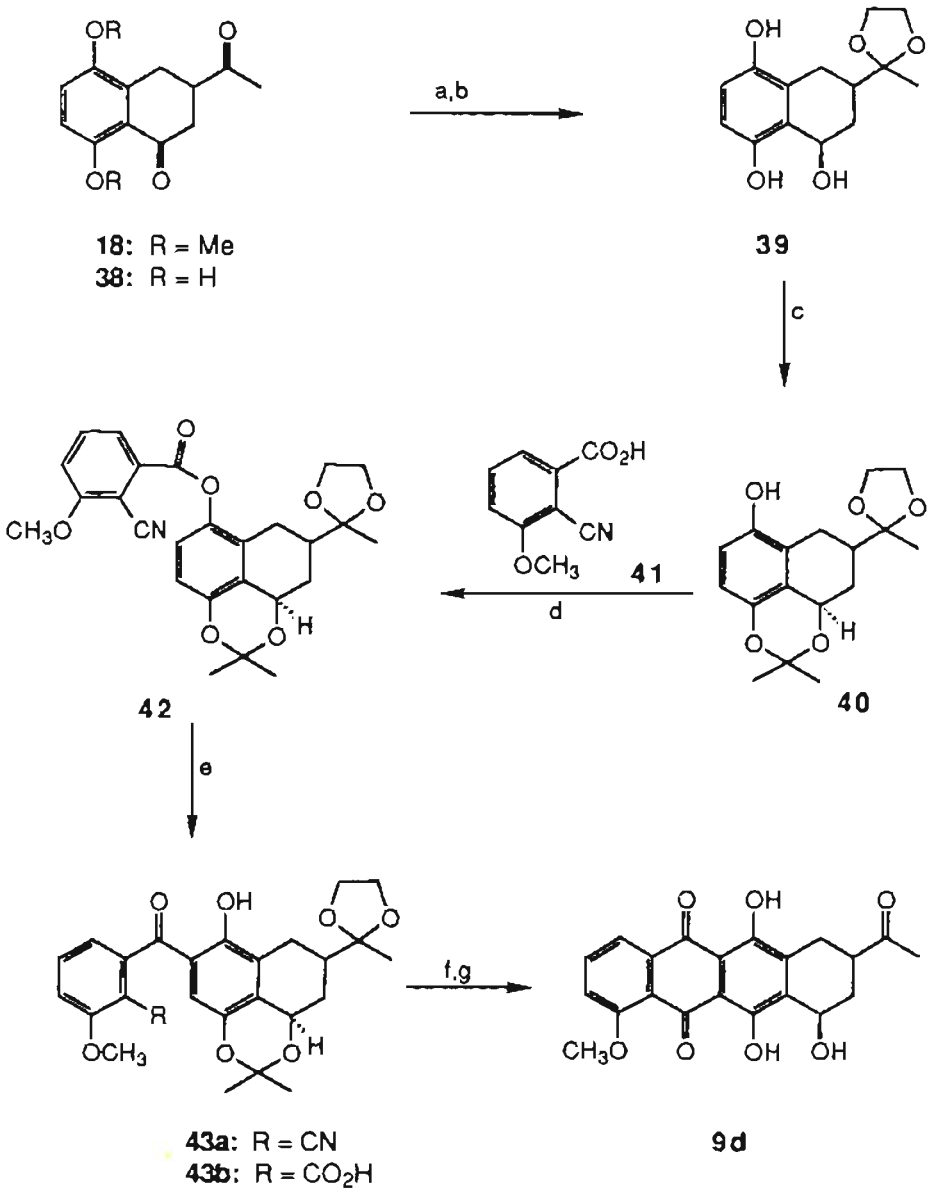
Although the Friedel-Crafts acylation and Diels-Alder cycloaddition reactions used in these early approaches provided reasonably straightforward approaches to daunomycinone, neither achieved the proper orientation between the A and D rings. It became clear that in order to accomplish the efficient synthesis of daunomycinone, methods for regiospecific construction of aromatic systems were needed.

1. Photo Fries Rearrangement

In 1975, Kende, et al., reported the first regiospecific synthesis of an intermediate to daunomycinone as shown in Scheme 1.5.[50] The key step in this preparation was photochemical Fries rearrangement of the ester **42** which regiospecifically furnished the ketone **43a**, thereby establishing the proper orientation between the A and D rings.

The dimethoxy tetralone **18** was demethylated to the phenolic intermediate **38** (76%). Selective ketallization of the acetyl carbonyl group, followed by sodium borohydride reduction of the benzylic carbonyl, furnished **39** in 76% overall yield. Treatment of **39** with 2,2-dimethoxypropane gave the unstable acetonide **40** in 88% yield. Acylation of the free phenol with 3-methoxy-2-cyanobenzoic acid gave **42** in 77% yield. Photochemical rearrangement of the ester **42** through irradiation of a 1% solution of **42** in dry dioxane was conducted until half of the starting material was consumed. Chromatography of the product gave a 48% yield of the ketone **43a** based on consumed ester and a 47% yield of the recovered ester. Hydrolysis of the cyano group in **43a** with sodium hydroxide, followed by intramolecular cyclization of the resulting keto acid **43b** with liquid hydrogen fluoride, furnished 9-deoxydaunomycinone (**9d**) in 23% yield. While the regiospecificity of the Fries rearrangement eliminated the problem of isomer formation, the process itself was inefficient, producing **9d** in an overall yield of only 2% from **18**.

Scheme 1.5 Kende's Regiospecific Synthesis



a. $HOCH_2CH_2OH$, TsOH b. $NaBH_4$ c. 2,2-Dimethoxypropane
d. $PhSO_2Cl$, Py e. hv f. NaOH g. HF

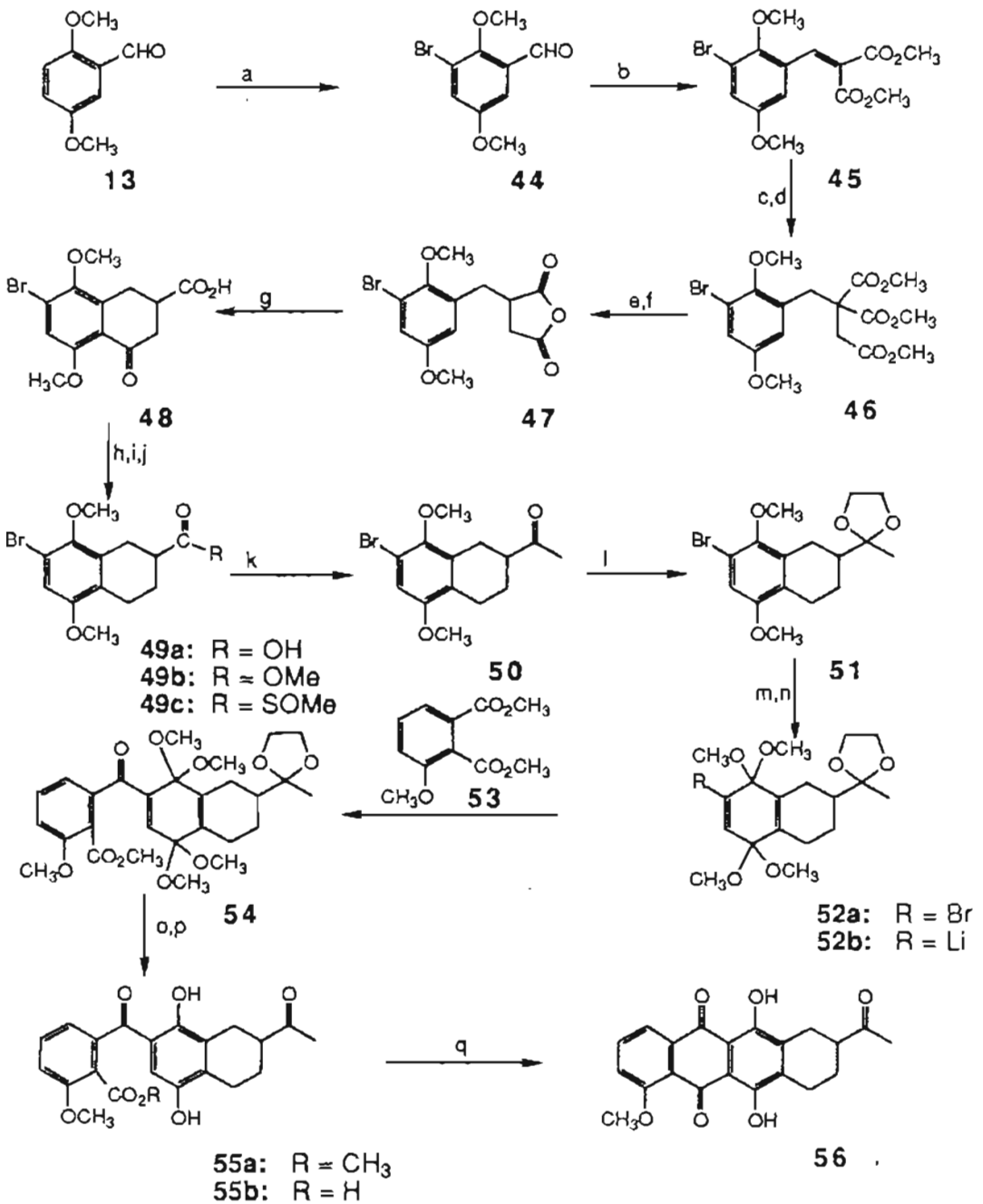
2. Acylation

In 1978, Swenton, *et al.*, reported the regioselective synthesis of 7,9-dideoxydaunomycinone shown in Scheme 1.6.[51] Regiochemical control was based on condensation of the lithiated intermediate **52b** with the less hindered carbomethoxy group of the phthalate **53** to furnish the ketone **54** which established the proper orientation of the A and D rings.

Bromination of dimethoxybenzaldehyde **13** gave **44**, which was then condensed with dimethyl malonate to give **45**. Conjugate reduction of the double bond in **45** with lithium tri-*sec*-butylborohydride followed by *in-situ* alkylation of the resulting anion with methyl bromoacetate gave the triester **46**. Conversion of **46** to the anhydride **47** was accomplished through saponification, decarboxylation, and dehydration in 84% overall yield from **46**. Intramolecular cyclization of **47** with hydrofluoric acid gave the keto acid **48** in 89% yield. Reductive removal of the ketone group in **48** was accomplished with triethylsilane and trifluoroacetic acid in 97% yield. Esterification of the acid in **49a** with diazomethane gave the ester **49b**, and then condensation of **49b** with dimsyl anion gave the sulfoxide **49c**. Reductive cleavage of the sulfoxide furnished the methyl ketone **50** in 82% overall yield from **49a**. Protection of the acetyl group in **50** through ketalization gave **51** in 95% yield.

Anodic oxidation of **51** on platinum in the presence of potassium hydroxide in methanol afforded the acid sensitive quinone bisketal **52a** in 85% yield. The lithiated intermediate **52b**, prepared through metal

Scheme 1.6 Swenton's Synthesis



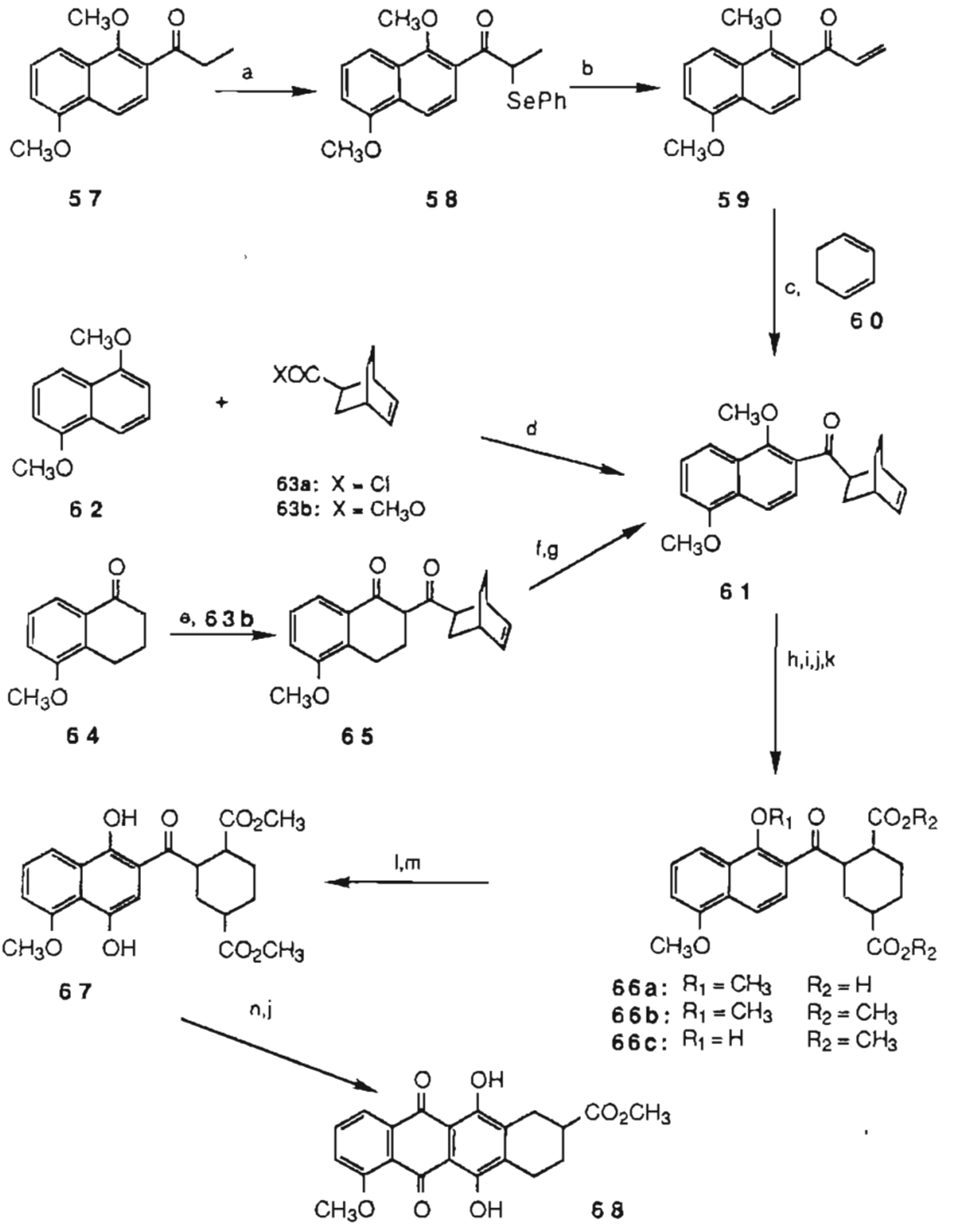
halogen exchange of **51a** with *n*-butyllithium, reacted selectively with the 3-carboethoxy functionality in **53** to give the keto ester **54** in 69% yield. Reductive hydrolysis of the ketal functionality in **54** with trifluoroacetic acid in the presence of stannous chloride furnished the keto ester **55a**. Saponification of the ester to the acid **55b**, followed by intramolecular Friedel-Crafts acylation with methanesulfonic acid, gave 7,9-dideoxydaunomycinone (**56**) in 40% yield from **54**.

Swenton's sequence permitted preparation of the dideoxydaunomycinone intermediate **56** in 14% overall yield from **44**. A number of steps could be performed without purification and no chromatography was required. While this was an impressive regioselective synthesis, its use as a preparative route was precluded because of the large number of steps and the instability of certain intermediates.

In the following year Sih, *et al.*, reported three different regiospecific approaches to the naphthalene intermediate **61**, which was then converted into the daunomycinone precursor **68** as shown in Scheme 1.7.[52] The inherent symmetry found in 1,5-disubstituted naphthalenes, such as **62**, assured that monoacylation adjacent to a methoxy group would give only one isomer.

In the first approach to the naphthalene derivative **61**, condensation of the anion of **57** with phenylselenyl bromide produced the selenide **58**. Hydrogen peroxide oxidation resulted in elimination of phenylselenic acid and gave the unsaturated ketone **59** in 73% overall yield. Diels-Alder cycloaddition of **59** with 1,3-cyclohexadiene (**60**) gave **61** in 94% yield. Alternatively, **61** could be prepared directly from

Scheme 1.7 Sih's Synthesis



a. LDA, PhSeBr b. H_2O_2, Py c. 140° C d. *n*-BuLi, TMEDA
e. Mesityllithium f. Chloranil g. Me_2SO_4 h. O_3, EtOAc, KI i. CrO_3, H_2SO_4
j. CH_2N_2 k. BBr_3 l. $Ce(NH_4)_2(NO_3)_6$ m. $Na_2S_2O_4$ n. H_2SO_4

1,5-dimethoxynaphthalene (**62**) through condensation of the lithiated anion of **62** with the ester **63b** or the acid chloride **63a**, though in only 15-20% yield. In the third route, the lithium anion of the tetralone **64** was condensed with the ester **63b** to give the diketone **65** in 51% yield. Chloranil oxidation, followed by methylation, gave the substituted naphthalene **61** in 83% yield.

The naphthalene intermediate **61** was converted into the diester **66c** in four steps. Ozonolysis of **61** gave a dialdehyde intermediate, which on Jones oxidation furnished the diacid **66a**. Esterification of **66a** with diazomethane gave the diester **66b**, which was demethylated with boron tribromide to give **66c** in 34% overall yield. Oxidation of **66c** with ceric ammonium nitrate, followed by dithionite reduction, produced the hydroquinone **67** in 45% yield. Cyclization of **67** with sulfuric acid and reesterification furnished the daunomycinone precursor **68** in 41% yield. Although this approach is regiospecific, the overall yield of **68**, based on the first route to the intermediate **61**, was only 4%.

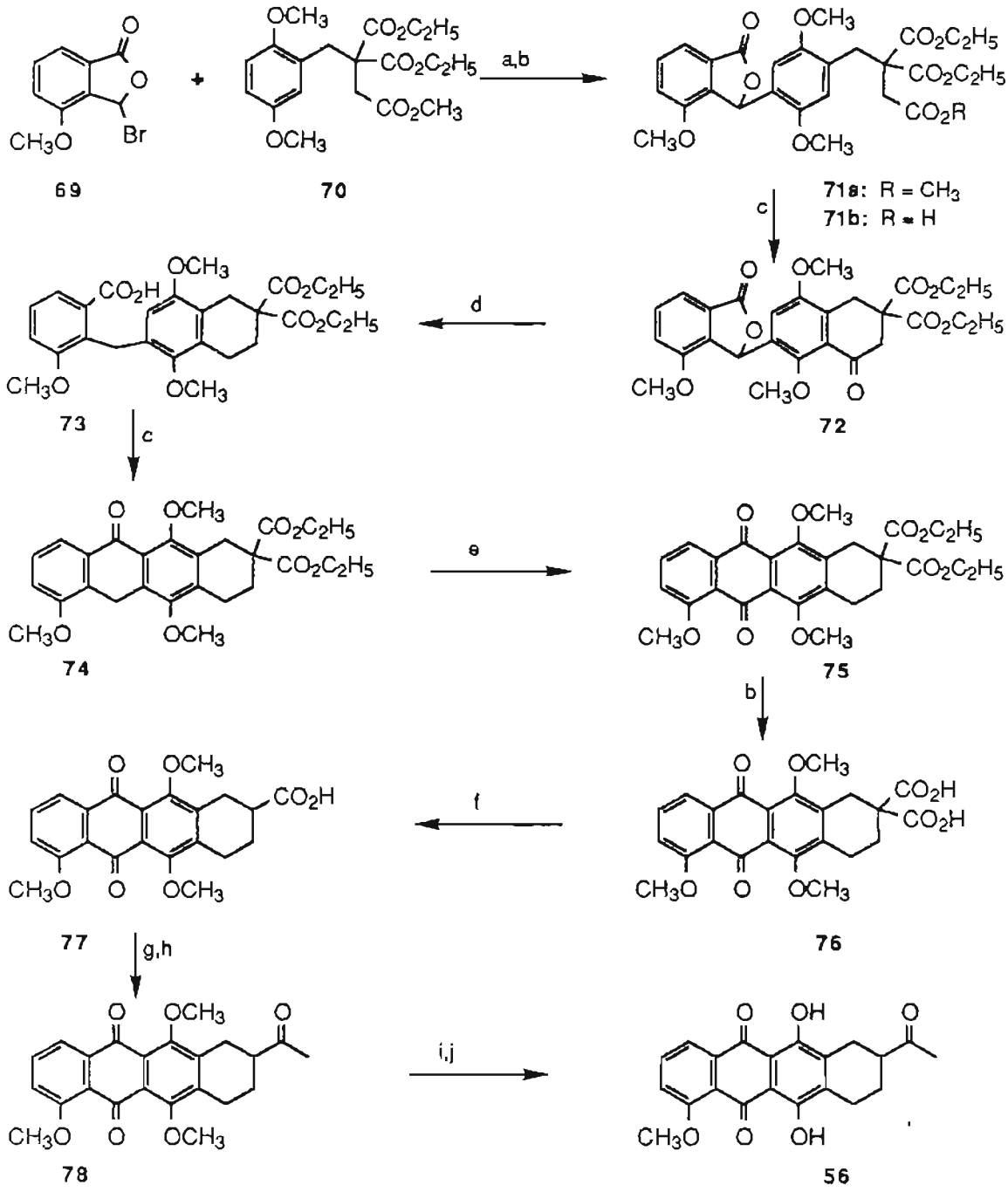
3. Alkylation

Johnson *et al.*, (1979) employed a regiospecific Friedel-Crafts alkylation for the synthesis of the daunomycinone intermediate **56** as shown in Scheme 1.8.[53] Regiocontrol in this synthesis was based on the *ortho* and *para* directing effects of the triester and methoxy groups in **70**. Alkylation of **70** with **69** occurred at the position which was *para* to the triester group. This position was favored because it was *para* to an alkyl

group and at the same time *ortho* to a methoxy substituent. One of the other possible positions was blocked due to steric hindrance while the remaining position was *meta* to both the triester alkyl group and a methoxy group.

Regiospecific condensation of 3-bromo-4-methoxyphthalide (**69**) with **70** gave **71a** in 94% yield. Saponification of the terminal ester in **71a** produced the acid **71b** (96%), which was cyclized with trifluoroacetic acid and trifluoroacetic anhydride to the tetralone **72** in 91% yield. Reductive removal of the ketone and cleavage of the phthalide in **72** was accomplished with triethylsilane in 92% yield. The resultant acid **73** was cyclized with trifluoroacetic anhydride and trifluoroacetic acid (88%) to the anthrone **74**. Oxidation of **74** with chromic acid furnished the quinone **75** in 62% yield. Saponification of the ester groups in **75** followed by decarboxylation of the resultant diacid **76** gave the acid **77** in 85% yield. The acid chloride derived from **77** was reacted with lithium dimethylcuprate (80%) to produce the acetyl product **78**. Selective demethylation of the B ring was performed in a two step process. Oxidation with silver(II) oxide was followed by reduction of the intermediate diquinone with diethylhydroxylamine which gave 7,9-dideoxydaunomycinone (**56**) in 83% yield. This route, employing simple reactions, provided the daunomycinone intermediate **56** in a relatively high 23% overall yield from **69** and **70**.

Scheme 1.8 Johnson's Synthesis



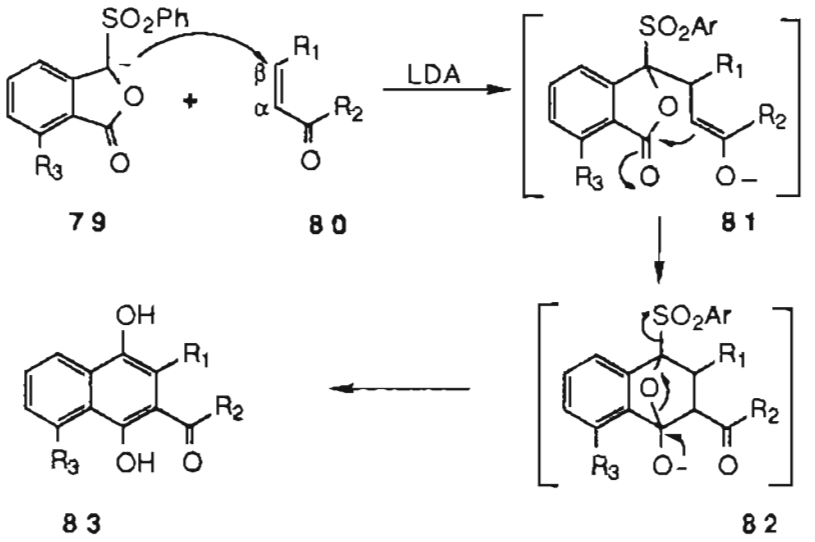
a. $SnCl_4$, CH_2Cl_2 b. KOH c. TFA, TFAA d. Et_3SiH, TFA e. CrO_3, H_2SO_4
f. Piperidine, AcOH g. $SOCl_2$ h. Lithium dimethylcuprate i. AgO, HNO_3 j. Et_2NOH

4. Michael Addition

During this same period, a number of researchers began reporting annelation methods based on directed carbanion condensation. Michael addition of stabilized anions to unsaturated carbonyl systems proved to be a highly regiospecific method for ring annelation.

Much of this newly emerging work was based on a carbanion condensation methodology reported by Hauser and Rhee. As shown in Scheme 1.9, Hauser and Rhee reported (1978) a method for regiospecific synthesis of substituted naphthalenes based on the condensation of phthalide sulfone anions with Michael acceptors.[54] The anionic intermediates **81** resulting from conjugate addition of the sulfones **79** with the Michael acceptors **80** underwent intramolecular acylation to give **82**. Loss of phenysulfinate and tautomerization of the resultant 1,4-diketone produced good yields of the 1,4-dihydroxynaphthalenes **83**. Unlike some of the previously mentioned methods, this methodology assures that condensation will occur only between specific reactive sites on the substrates. The nature of the Michael reaction dictates that addition of the anion of the sulfone to the Michael acceptor will occur specifically at the β unsaturated carbon. It then follows that intramolecular acylation can take place only between the α enolate carbon and the ester carbonyl of the sulfone. Thus the orientation between the R_1, R_2, R_3 substituents on the naphthalene **83** can be strictly controlled.

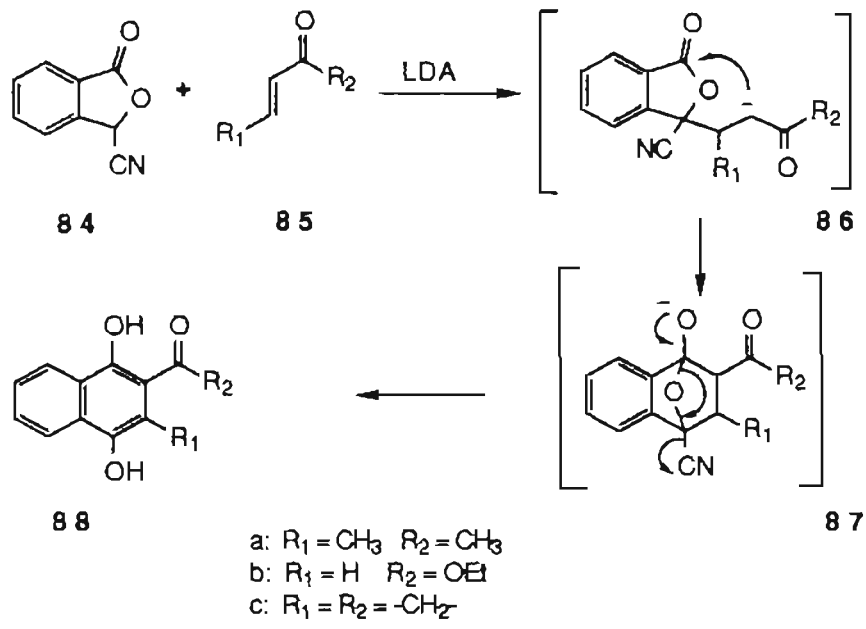
Scheme 1.9 Hauser and Rhee



	R_1	R_2	R_3	% Yield
a	H	OEt	H	32
b	H	Me	H	29
c	Me	OEt	H	70
d	Me	Me	Me	68
e	Me	Me	H	86
f	$-CH_2-$		H	69

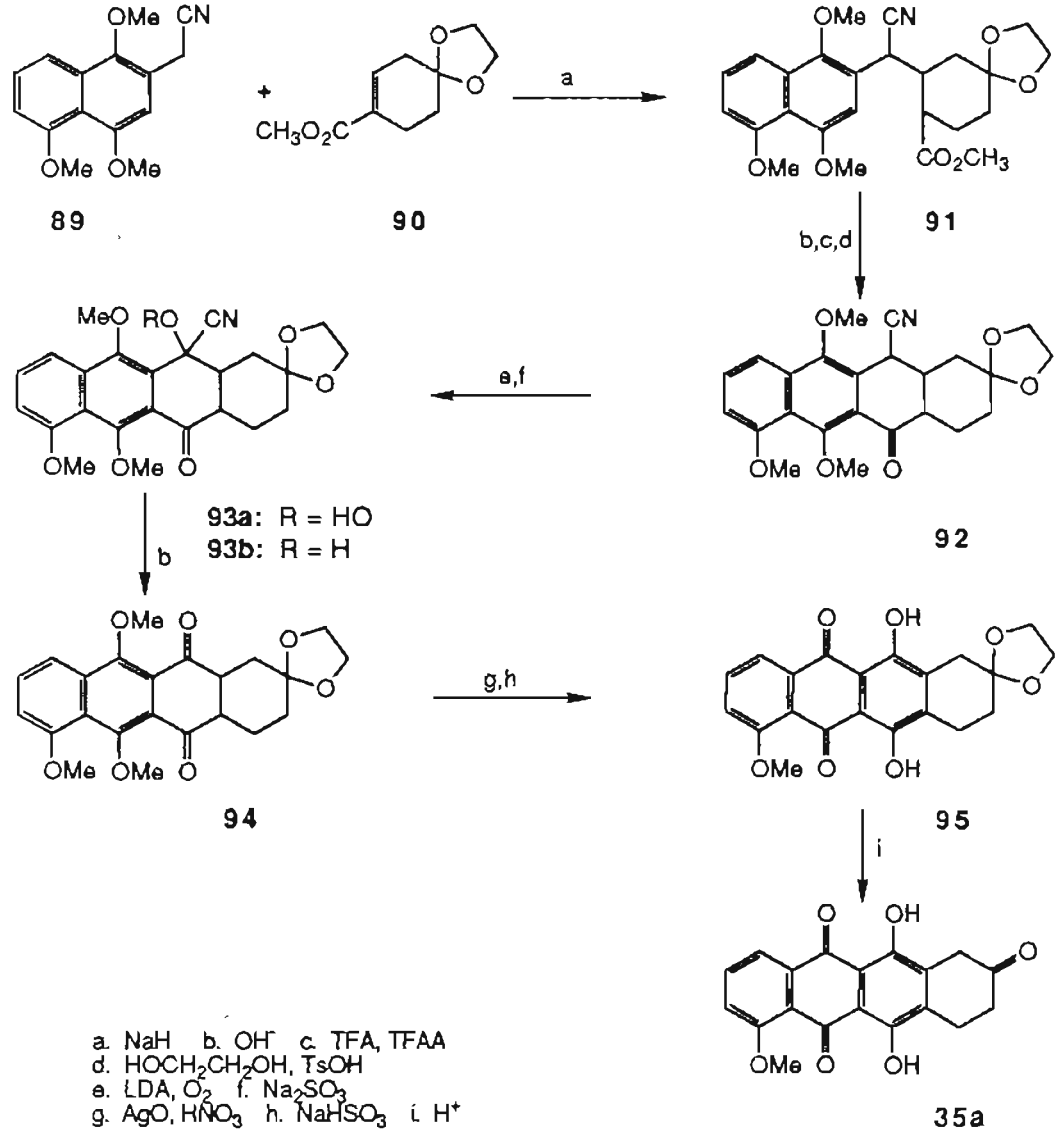
In the same year Kraus and Sugimoto reported a similar method based on the use of phthalide nitriles as shown in Scheme 1.10.[55] Conjugate addition of the the anion of the nitrile phthalide **84** to substituted unsaturated carbonyl compounds **85** gave the dihydroxy-naphthalenes **88**.

Scheme 1.10 Krauss' Synthesis



In 1979, Kende, *et al.*, reported the regiospecific synthesis of the daunomycinone precursor **35a** based on the Michael reaction shown in Scheme 1.11.[56] Regiospecific Michael addition of the anion of the nitrile **89** to the unsaturated ester **90** gave the condensation product **91** in 94% yield. Saponification (85%) of **91**, followed by intramolecular Friedel-Crafts cyclization and then reketallization, produced the nitrile **92** in 89% yield. The anion of the nitrile **92** was reacted with oxygen and the resultant hydroperoxy intermediate **93a** was reductively cleaved with bisulfite to give the cyanohydrin **93b**. Elimination of cyanide from **93b** furnished the *leuco*-quinone **94** in 70% yield. Oxidative demethylation of **94** with silver(II) oxide followed by bisulfite reduction of the diquinone intermediate gave the quinone **95**. Hydrolysis of the ketal in **95** furnished

Scheme 1.11 Kende's Michael Addition Synthesis

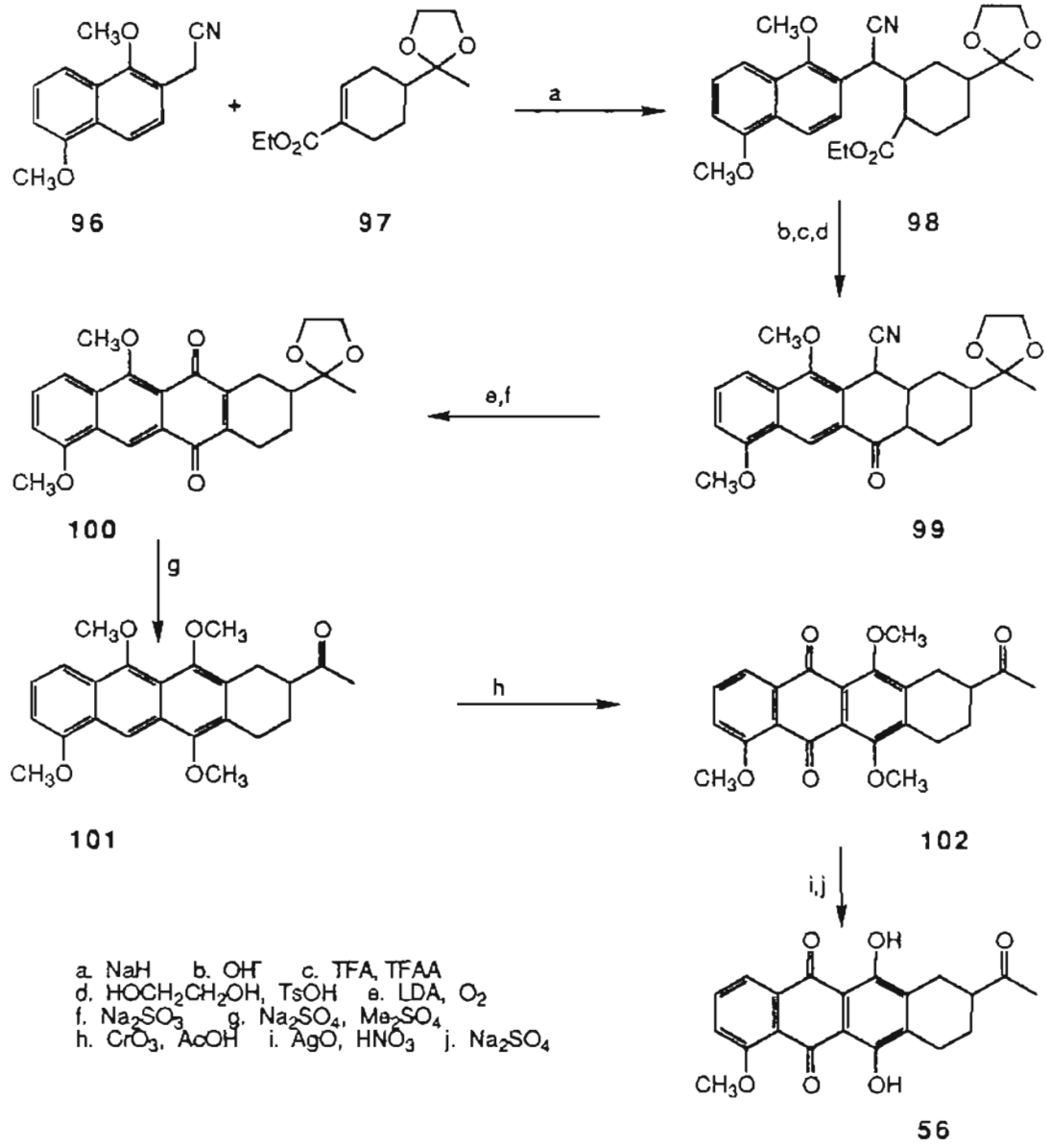


35a (70% yield from **94**), which previously had been converted into daunomycinone. The above sequence produced **35a** in 32% overall yield; however, subsequent low yield conversion of **35a** to daunomycinone, as was reported previously by Kende,[49] allowed for only a 3% overall yield.

The following year Parker and Kallmerten employed the same strategy with different substrates and accomplished the synthesis of 7,9-dideoxydaunomycinone shown in Scheme 1.12.[57] Regiospecific condensation of the nitrile **96** with the unsaturated ester **97** gave the nitrile **98** in 60% yield. Saponification of **98**, cyclization of the resulting acid, and then reketallization gave the nitrile **99**. Kende's method was employed to oxidatively transform **99** into the quinone **100**. Reductive methylation of **100** with sodium bisulfite and dimethylsulfate gave the tetramethoxy intermediate **101**. Oxidation of **101** with chromium trioxide in acetic acid produced the quinone **102**. Oxidative demethylation of the B ring in **102** furnished 7,9-dideoxydaunomycinone (**56**) in 47% yield from **100**. The above sequence gave 7,9-dideoxydaunomycinone in 22% overall yield from **96** and **97**.

The above two syntheses demonstrated that the Michael reaction can be used to regiospecifically fabricate precursors to daunomycinone. In addition, various substrates can be used as Michael acceptors and donors. As was observed above, the choice of substrates can be an important factor governing the efficiency of these syntheses. Parker and Kallmerten's use of the ketal protected acetyl substituted Michael acceptor **97** proved to be a more efficient route to daunomycinone.

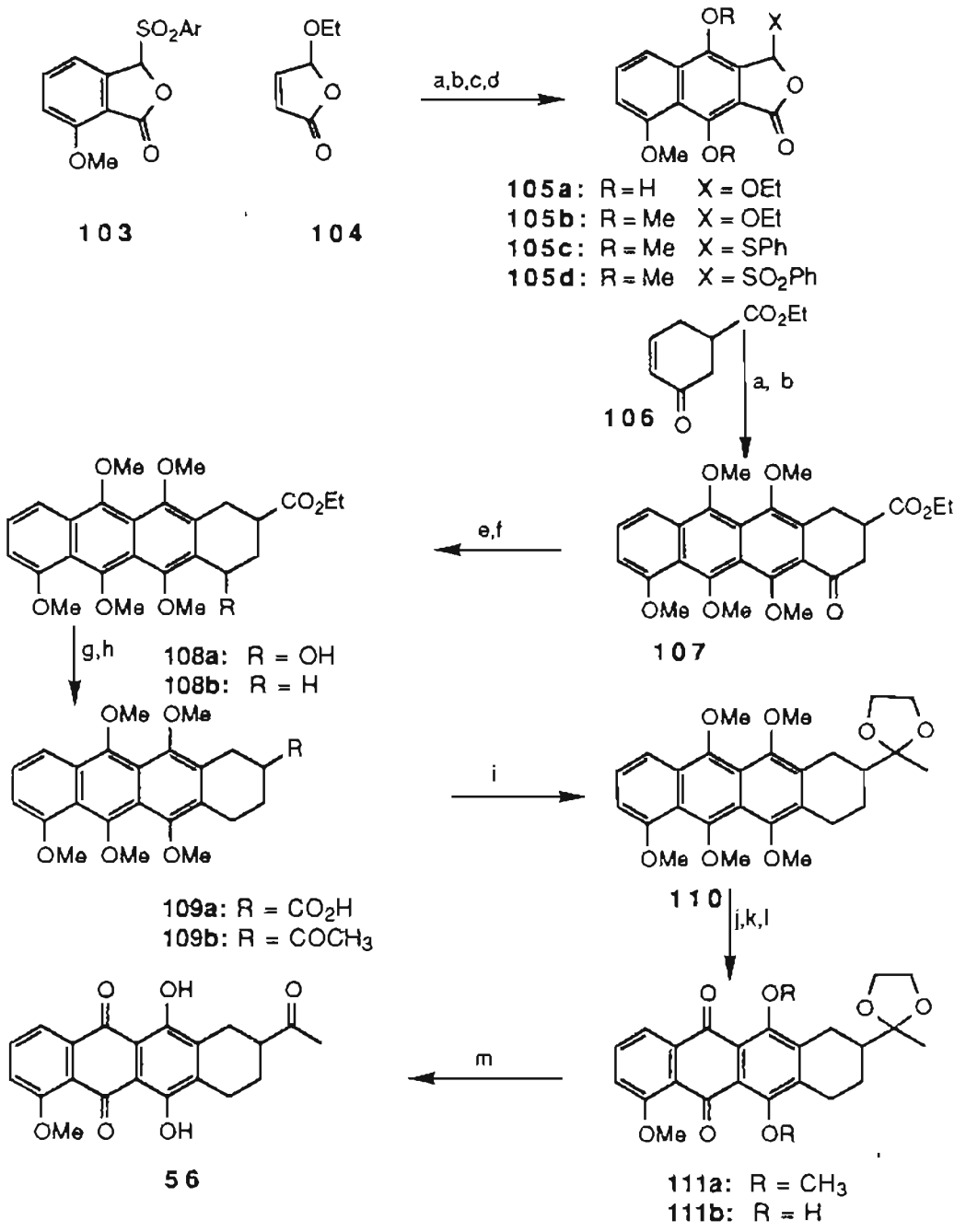
Scheme 1.12 Parker's Synthesis



Utilizing the phthalide sulfone condensation methodology, Hauser and Prasanna reported (1981) two regiospecific linear routes to 7,9-dideoxydaunomycinone intermediates.[58] One of these routes is shown in Scheme 1.13. The strategy consisted of iterrative annelation of phthalide sulfones with different unsaturated carbonyl components.

Condensation of methoxyisobenzofuranone **103** with 5-ethoxy-2(5H)-furanone (**104**) gave **105a**, which upon methylation, furnished the naphthofuranone **105b** in 74% overall yield. The ethoxyfuranone fragment served as a latent functionality for regeneration of the phenyl sulfonyl furanone fragment. Reaction of **105b** with benzenethiol produced the thiophenyl naphthofuranone **105c**, which was then oxidized with *meta*-chloroperbenzoic acid to the sulfone **105d** in 88% overall yield. Condensation of the anion of **105d** with 5-carboethoxy-2-cyclohexenone (**106**) yielded, after methylation, the naphthacene **107** (85%). A two step process was used to reductively remove the ketone in **107**. Reduction of **107** to the alcohol **108a** was followed by removal of the alcohol moiety with triethylsilane and trifluoroacetic acid and furnished **108b** in 85% overall yield. Saponification of **108b** to the acid **109a**, and reaction of the resultant carboxylate anion with methyllithium gave the methyl ketone **109b** in 92% overall yield. The ketal **110**, obtained from **109b**, was treated with ceric ammonium nitrate and pyridine carboxylic acid to oxidatively cleave the 5,12-dimethoxy groups and furnish the quinone **111a** in 96% yield. The 6,11-dimethoxy groups were oxidatively cleaved with silver(II) oxide and then reductive workup gave **111b** in 95% yield. Hydrolysis (94%) of the ketal group in **111b** gave 7,9-dideoxy-

Scheme 1.13 Hauser and Prasanna's Synthesis



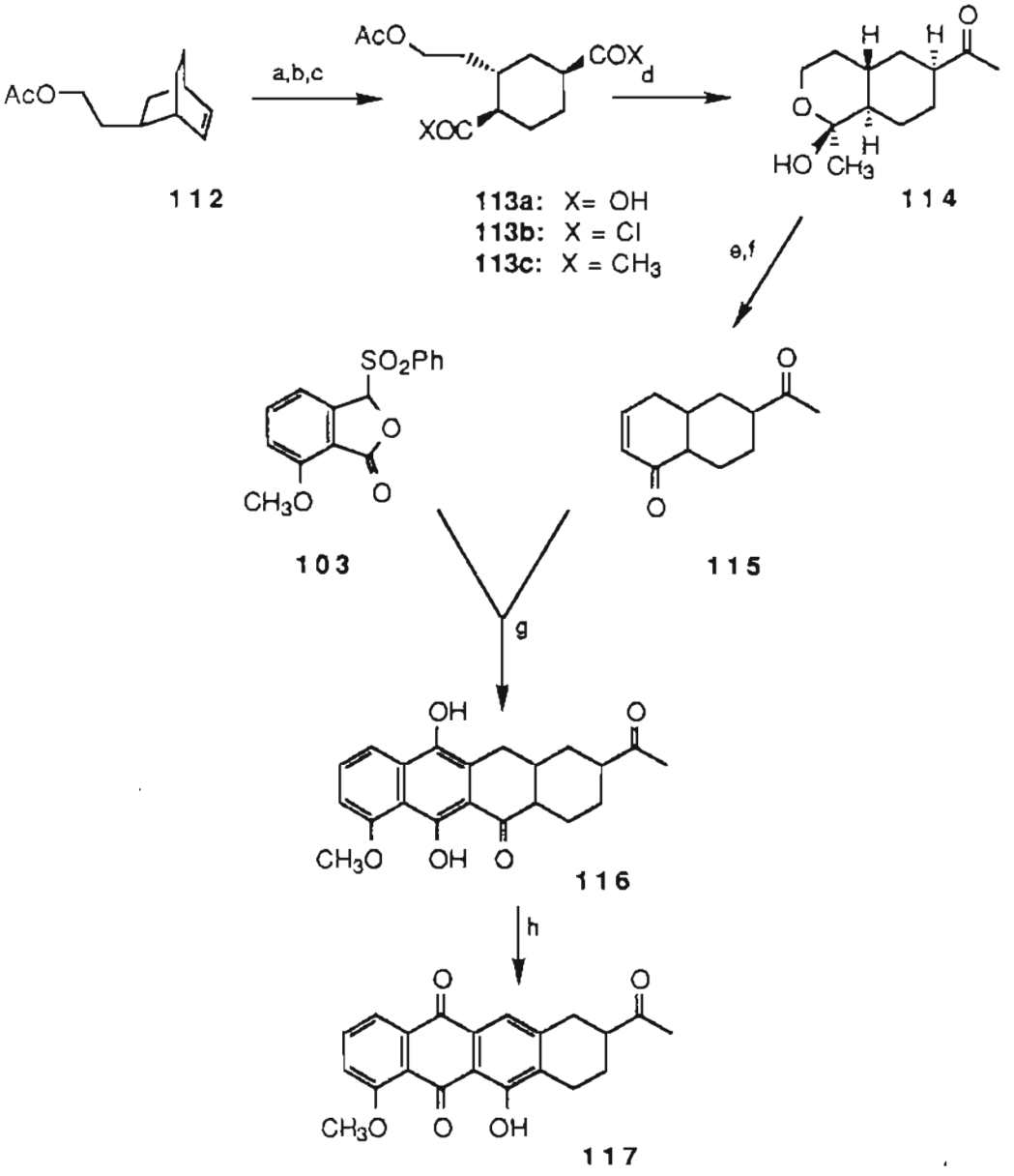
a. LDA b. Me_2SO_4 c. PhSH, TsOH d. MCPBA e. $NaBH_4$
f. Et_3SiH, TFA g. KOH h. LiH, MeLi i. $HOCH_2CH_2OH$, TsOH
j. $Ce(NH_4)_2(NO_3)_6$, Pyridine carboxylic acid N-oxide
k. AgO, HNO_3 l. $NaHSO_3$ m. H^+

daunomycinone (**56**). This sequence gave **56** in 37% overall yield from **103** and **104**, which when compared with the previously mentioned syntheses, was excellent. Furthermore, the linear approach allowed the use of easily prepared Michael acceptor substrates.

In 1983, Hauser and Mal reported the convergent synthesis of the 11-deoxydaunomycinone precursor **117** shown in Scheme 1.14.[59] The use of the naphthalenone **115** as the Michael acceptor permitted generation of the tetracyclic intermediate **116** in one step.

The naphthalenone **115** was prepared from the bicyclic acetate **112**. Ruthenium tetraoxide cleavage of the double bond in **112** gave the diacid **113a** in quantitative yield. Conversion of **113a** to the diacid chloride **113b**, followed by treatment with lithium dimethylcuprate, gave the diketone **113c** in 74% yield. Hydrolysis of the acetate in **113c** furnished the hemiketal **114** in 59% yield. Oxidation of **114** furnished a keto aldehyde intermediate which upon intramolecular aldol cyclization and dehydration gave the naphthalene **115** in 50% yield. Condensation of the anion of the sulfone **103** with **115** gave the tetracyclic intermediate **116** in 96% yield. Aromatization of **116** to 7,9,11-trideoxydaunomycinone (**117**) was accomplished in near quantitative yield by heating **116** in dimethylformamide under an oxygen atmosphere. This procedure proved to be brief and efficient and the convergent approach led to a tetracyclic intermediate in just one step from **103** and **115**. Both the condensation of the sulfone with the naphthalenenone and the oxidation to the anthraquinone were high yield steps.

Scheme 1.14 Hauser and Mal's Synthesis



a. RuO_4, $NaIO_4$, Acetone b. $SOCl_2$ c. Me_2CuLi, Et_2O d. NaOH
e. $CrO_3 \cdot 2Py$, CH_2Cl_2 f. HCl, THF g. $LiOBu^t$, THF h. O_2, DMF, Δ

III. Synthesis

A. Strategy

The previous section described an efficient preparation of an 11-deoxydaunomycinone intermediate. Introduction of an oxygen at the C-11 position of either **116** or **117** would enable the preparation of daunomycinone. An attractive feature of this strategy is that access to either anthracycline from a common intermediate would be possible.

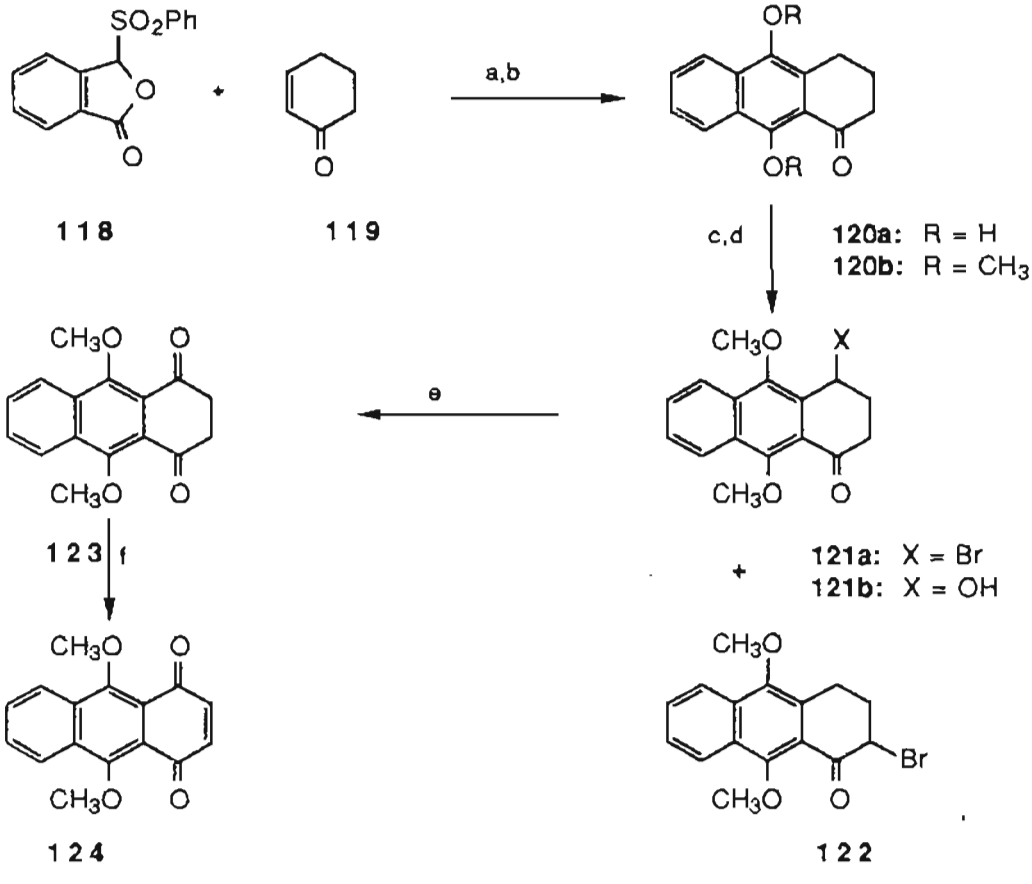
While hydroxylation of **117** is possible, studies by others have shown that the yield is generally rather modest.[60] A reasonable alternative would be introduction of an oxygen functionality in **116** through benzylic bromination-solvolysis.

B. Model Studies

With this premise, we undertook the model study shown in Scheme 1.15. MacKay had reported earlier that bromination of **120b** in carbon tetrachloride with azobisisobutyronitrile either in the dark or under a sunlamp gave exclusively the bromoketone **122** in 92% yield.[61] For our studies, the hydronaphthacenone **120a** was conveniently prepared through phthalide sulfone condensation of the sulfone **118** with 2-cyclohexenone followed by methylation with dimethyl sulfate.[54]

Initial studies showed that photochemically induced free radical bromination of **120b** with N-bromosuccinimide (NBS) in carbon tetrachloride, with benzoylperoxide as an initiator, gave a mixture of the desired benzylic bromination product **121a** and undesired bromoketone **122**. In marked contrast to the above results, it was found that photochemical bromination of **120b** with NBS in carbon tetrachloride in

Scheme 1.15 Model study



a. $LiOBu^t$, THF b. Me_2SO_4, K_2CO_3 c. NBS, CCl_4, light
d. H_2O, THF e. $CrO_3 \cdot 2Py$, CH_2Cl_2 f. SeO_2, CH_2Cl_2

the absence of any free radical initiators gave exclusively the benzylic bromination product **121a**.

Hydrolysis of **121a** with water in tetrahydrofuran (THF) gave the hydroxy product **121b** in 65% yield. Collins oxidation[62] furnished the *leuco*-quinone **123** (67%). ^{1}H-NMR showed a methylene resonance for **123** at 3.05 ppm (δ) and no phenolic absorptions for the tautomeric phenol. Dehydrogenation of **123** with selenium dioxide[63] furnished the quinone **124** in 90% yield.

C. Naphthalenone

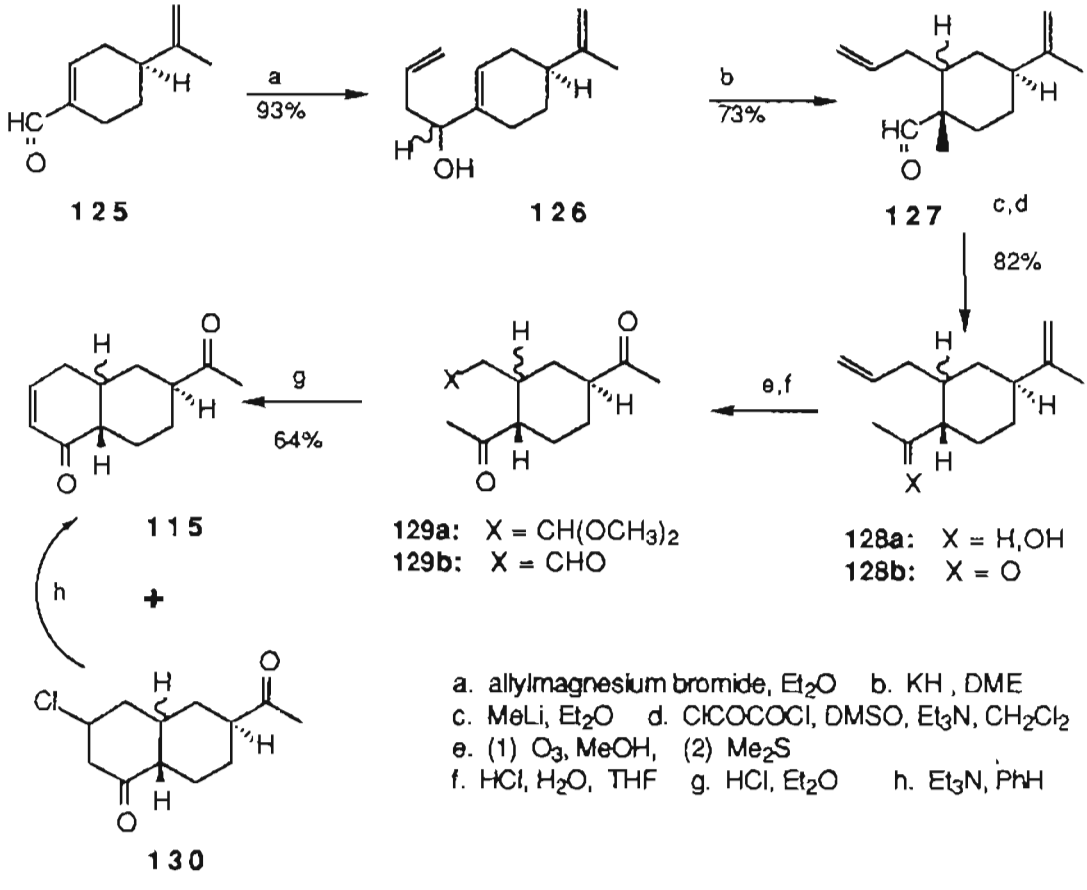
Having satisfied the objective that selective introduction of an oxygen at C-11 could be accomplished, we set out to perform a synthesis of 7,9-dideoxydaunomycinone. Although the required acetylnaphthalenone **115** had been previously prepared,[59] we desired an alternate approach capable of producing this material in fifty gram quantities. Previously, lithium dimethyl cuprate was used to convert the diacid chloride **113b** to the diketone **113c** (Scheme 1.14). However, this procedure required working at low temperature with a sensitive and sparingly soluble reagent. The use of simple chemical transformations which would not require stringent reaction conditions would be most desirable, since it would make the synthesis easier and more amendable for large scale preparation.

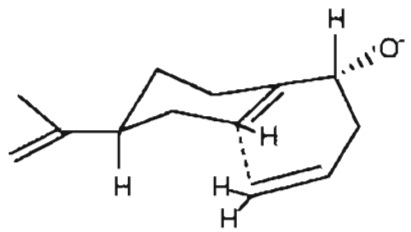
Synthesis of the naphthalenone was performed from commercially available (*l*)-perilaldehyde (Scheme 1.16). The isopropylidene group in

perilaldehyde would serve as latent functionality for the acetyl group. The enone fragment would permit elaboration of the second ring.

Grignard addition of allylmagnesium bromide to perilaldehyde gave the homoallyl alcohol **126** (98%), which upon oxy-Cope rearrangement[64] with potassium hydride furnished the aldehyde **127** (73%) as a 1:1 mixture of isomers. The oxy-Cope rearrangement probably proceeds through the chair transition state with the alkoxide oxygen in the equatorial position, as shown in Figure 1.10. This would maintain

Scheme 1.16 Naphthalenone Synthesis





126b

Figure 1.10 Oxy-Cope Rearrangement

the stereochemical integrity of **126**;[64b] however, addition of the Grignard reagent to the aldehyde can occur from either face to produce two diastereoisomers. Addition of methyllithium to **127**, followed by Swern oxidation[65] of the alcohol intermediate **128a**, gave the ketone **128b** in 83% overall yield. Cleavage of both the isopropylidene and the allyl functionality in **128** through ozonolysis in methanol, with reductive workup using dimethyl sulfide, furnished the keto dimethyl acetal **129a** in 95% crude yield. The acetal structure was indicated by the ^{1}H-NMR spectrum which showed no aldehyde hydrogen resonance. Rather, there was a 1-H multiplet at 4.2-4.6 ppm (δ) due to the acetal hydrogen. Two procedures were developed to effect aldol cyclization and dehydration of **129a** to **115**. Simply treating a THF solution of **129a** with aqueous hydrochloric acid, then saturating with sodium chloride and refluxing for a couple hours gave, after chromatography, the acetyl naphthalenone **115** in about 52% yield. This method proved to be somewhat irreproducible and a more reliable procedure was developed. Brief treatment of

129a with dilute hydrochloric acid in THF quantitatively furnished the aldehyde **129b**. Intramolecular aldol cyclization[66] and dehydration was accomplished with dry hydrogen chloride in ether. This process yielded a mixture of **115** and the hydrogen chloride adduct **130**. Brief treatment of the crude product with triethylamine in refluxing benzene effected dehydrohalogenation of **130** to the naphthalenone **115** in 64% overall yield from **129a**. Because **115** was a mixture of *cis* and *trans* isomers, purification through fractional crystallization was tedious. Ultimately, distillation or repeated extraction of the crude product with hot hexane, proved to be more expedient.

This sequence was used to prepare 50 grams of **115** in 36% overall yield from **125**. The sequence was practical and adaptable to large scale preparation and all of the intermediates and final product are purified by distillation. The first three steps were simple and straightforward reactions conducted at near room temperature or at reflux. Although the Swern oxidation was conducted at -60 °C, the use of dimethyl sulfoxide and oxalyl chloride as oxidizing reagents makes it a very economical and efficient procedure. Ozonolysis was also conducted at -60 °C; however, the reaction is easily performed, even on a large scale. It has been shown recently, that cyclization of compounds similar to **129a** can be accomplished efficiently without the formation of chlorinated by-products by use of perchloric acid in aqueous tetrahydrofuran.[67] .

D. Daunomycinone

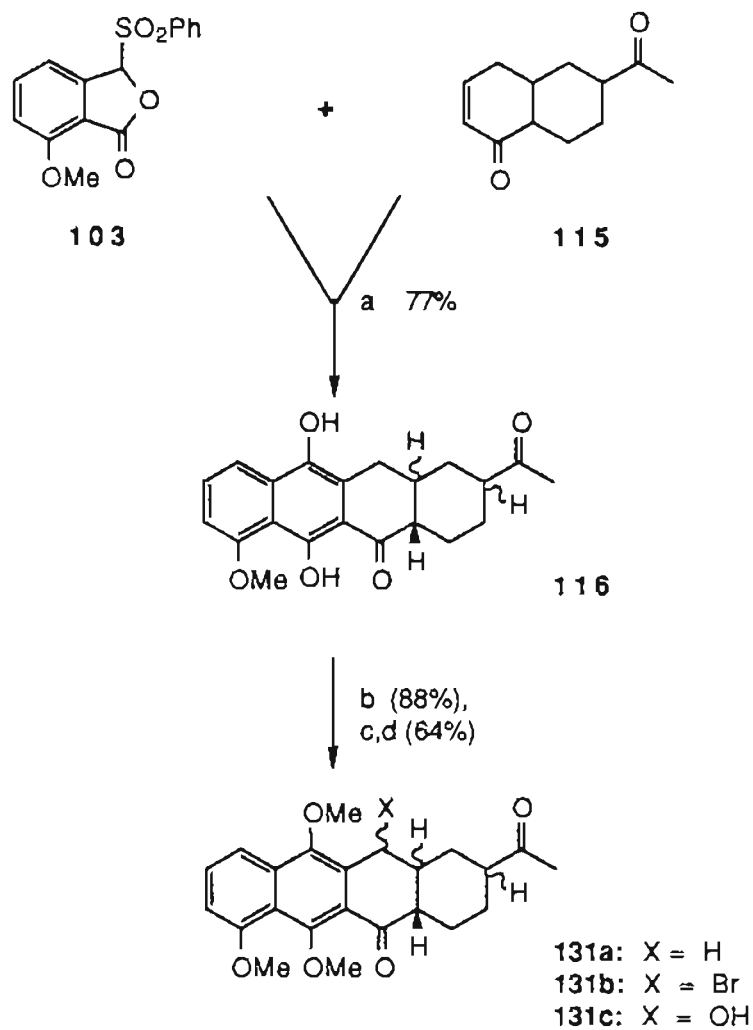
Using the naphthalenone **115**, preparation of racemic 7,9-dideoxy-daunomycinone, via the intermediacy of **116**, was undertaken as shown in Schemes 1.17 and 1.18.

Condensation of the naphthalenone **115** with the phthalide sulfone **103** produced the hydronaphthacenone **116** in 77% yield.[54,58-59] Purification of **116** was performed by exploiting its striking insolubility. Acidification and partial concentration of the THF reaction solution led to precipitation of impure **116**. Treatment of the impure product with boiling acetone and then filtration yielded pure **116** as a yellow powder. Because of the insolubility of **116** in pure $CDCl_3$, its ^{1}H-NMR spectrum could not be recorded; however, addition of a couple drops of trifluoracetic acid to a chloroform suspension of **116** caused it to solubilize completely and an excellent spectrum was obtained.

Methylation of **116** with dimethyl sulfate and potassium carbonate in dry refluxing 2-butanone gave the dimethyl ether **131a** in 88% yield. A ^{1}H-NMR spectrum showed **131a** to be a mixture of *cis* and *trans* isomers. Although treatment of a sample with sodium hydroxide in ethanol produced the all *trans* isomer, the isomeric mixture was used in the remaining steps. Homolytic bromination of **131a** with NBS in refluxing carbon tetrachloride under sun lamp irradiation gave the C-11 bromide **131b**. Hydrolysis of the bromide **131b** in aqueous THF, followed by

chromatography of the crude product on florisil, gave the alcohol **131c** as an isomeric mixture in 60-70% yield.

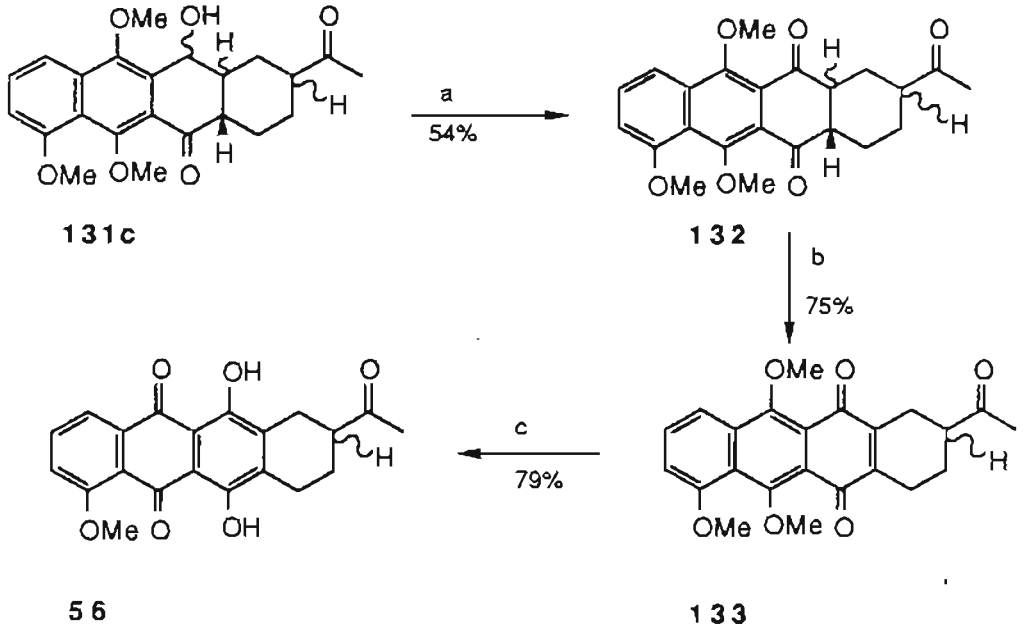
Scheme 1.17 Daunomycinone Synthesis



a. $LiOBu^t$, THF b. K_2CO_3, Me_2SO_4, MEK
c NBS, CCl_4 d. H_2O, THF

Collins oxidation[62] of **131c** (Scheme 1.18) gave the *leuco*-quinone **132** in 54% yield. The *leuco*-quinone **132** was dehydrogenated with selenium dioxide[63] to the crystalline orange quinone **133** in 75% yield. Selective cleavage of the 5,12-methyl ethers in **133** with boron trichloride[68] furnished 7,9-dideoxydaunomycinone (**56**) as red crystals in 79% yield. This material was identical with a sample prepared by a different route,[58] as evidenced by comparison of the ^{1}H-NMR spectrum and the melting point.

Scheme 1.18 Daunomycinone Synthesis



a. CrO_3-2Py, CH_2Cl_2 b. SeO_2, CH_2Cl_2 c. BCl_3, CH_2Cl_2

The new approach is notably brief and produces 7,9-dideoxy-daunomycinone (**55**) in 7 steps from **103** and **115** in 15% overall yield. This is contrasted with the 15 step (37% overall yield) for the linear approach performed earlier by Hauser and Prasanna (Scheme 1.15). With the exception of the bromination reaction, all the steps can be performed on a large scale to produce gram quantities of product. While this route gave a lower overall yield than the linear route, the brevity of the approach significantly increased its attractiveness.

The lower yield was principally due to the bromination, hydrolysis, and oxidation sequence. The intermediate **131c** is somewhat sensitive due to the presence of the benzylic hydroxyl group. The Collins reagent was employed because of its compatibility with acid sensitive substrates. However, the required use of a large excess of the reagent made isolation of the product somewhat difficult due to the presence of the large amount of precipitated chromium salts.

In summary, the new route to the naphthalenone **114** is highly successful. The sequence is experimentally nontedious and permits preparation of moderately large quantities of 7,9-dideoxydaunomycinone.

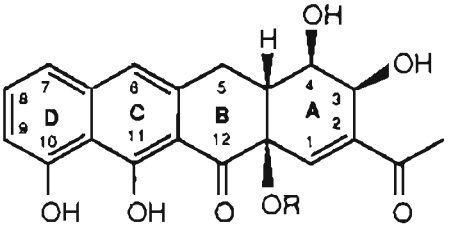
Part II: PILLAROMYCINONE

I. Introduction

A. Description

The pillaromycins, first reported by Shibata, *et al.*, in 1964, were isolated from *Streptomyces flavoviren* # 65786.[69] Of the four pillaromycins that were isolated, A_1,B_1,B_2,C_1, pillaromycin A_1 was the most active, possessing antibacterial and antitumor activities.

Pillaromycin A_1, shown in Figure 2.1, consists of a tetracyclic aglycone, pillaromycinone (**140a**), and the glycoside pillarose. Pillarose is a rather unusual sugar in that it possesses a hydroxyacetyl at the C-4



140a: Pillaromycinone **R = H**

140b: Pillaromycin A **R =**

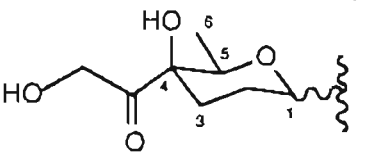
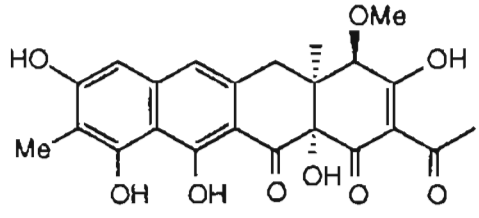


Figure 2.1

position of a 2,3,6-trideoxy-*l*-*threo*-aldohexose. Pillaromycinone is structurally similar to the commercially and medically important tetracyclines and in particular to chromocyclin which also has a naphthalene chromophore (Figure 2.2).[70]



141 Chromocyclin

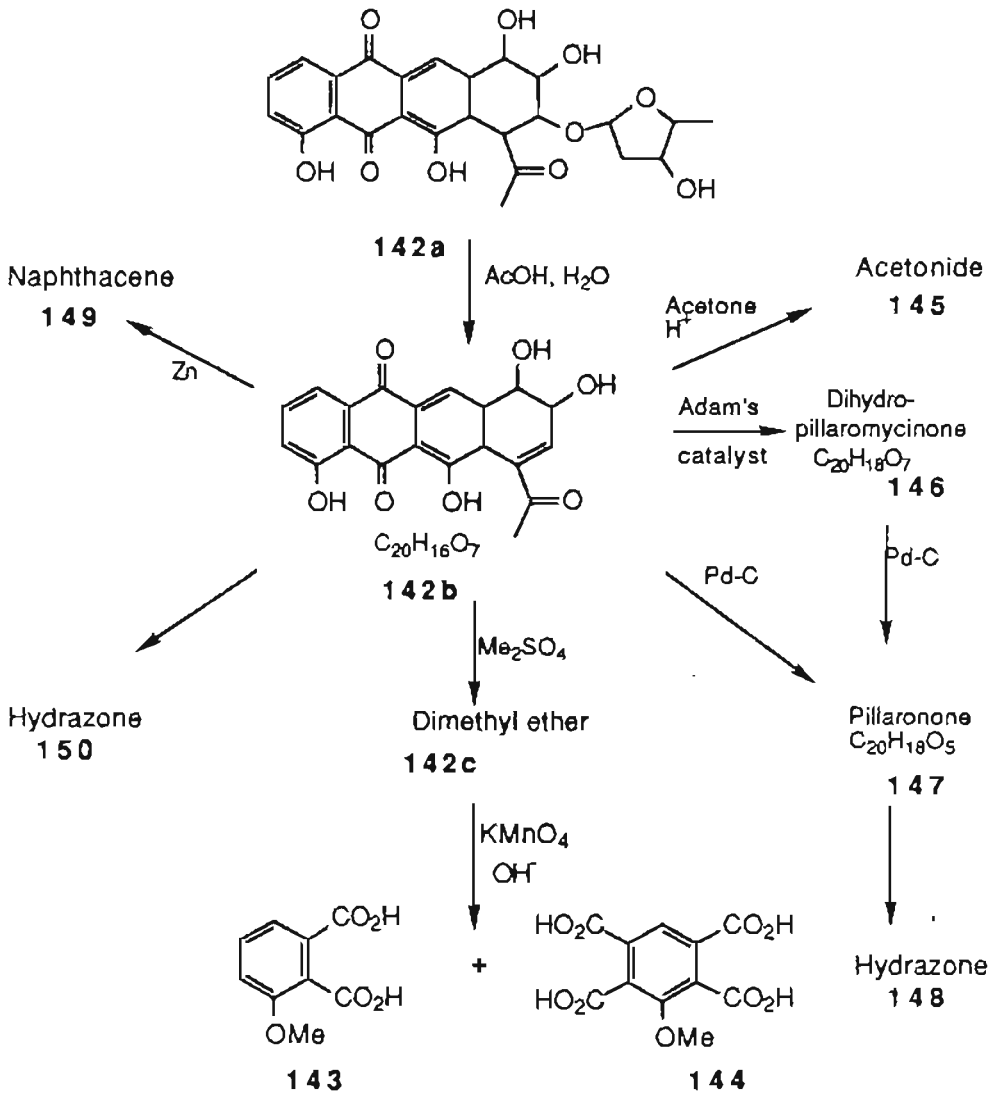
Figure 2.2

Like chromocyclin, pillaromycinone has a tetracyclic hydrocarbon skeleton containing a polyhydroxy naphthalene chromophore. A further similarity is the presence of a *cis*-fused ring juncture between the two nonaromatic rings, which though common among the tetracyclines, is unusual since *trans*-fusion of six membered rings is more stable. An acetyl at C-2, a carbonyl at C-12, a tertiary hydroxyl at C-12a, and two phenolic hydroxyls at C-10 and C-11 are also similar to the chromocycline structure. Pillaromycinone differs from tetracyclines in that it possesses a *cis*-diol on the convex face of the A ring and a double bond at the C-1,2 position. The stereochemistry of pillaromycinone consists of four contiguous chiral centers at C-3, C-4, C-4a, and C-12a with the three hydroxyl groups all *cis* to one another on the convex face.

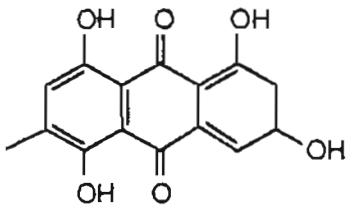
B. Structure Elucidation

The structures **142a** and **142b**, shown in Scheme 2.1, were initially proposed for pillaromycin A and pillaromycinone by Shibata *et al.*,[69] in

Scheme 2.1 Shibata's Degradations



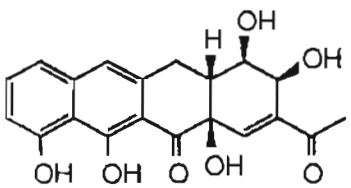
1964. The basis for assignment of this unusual structure was the ultraviolet spectrum, which was similar to that of flavoskyrin[71] (Figure 2.3). Infrared, NMR, and degradation studies supported the initially proposed structure.



151: Flavoskyrin

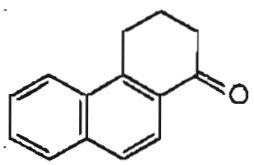
Figure 2.3

In 1970, Asai and coworkers revised the structure of pillaromycinone to **140a** (Figure 2.4).[72-75] This revision was based upon the similarity of the ultraviolet spectrum of **140a** to 1,2,3,4-tetrahydro-1-oxophenanthrene (Figure 2.5).[73,76] Additional NMR studies also supported



140a: Pillaromycinone

Figure 2.4

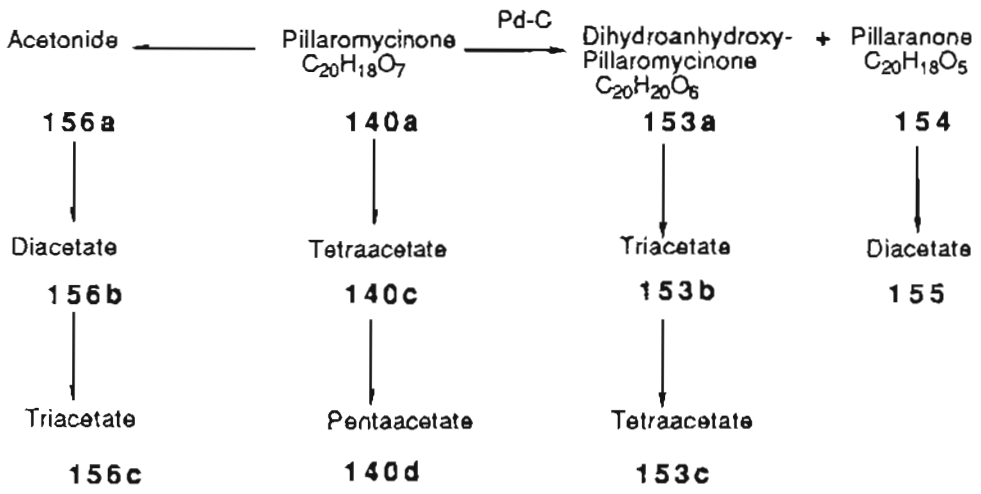


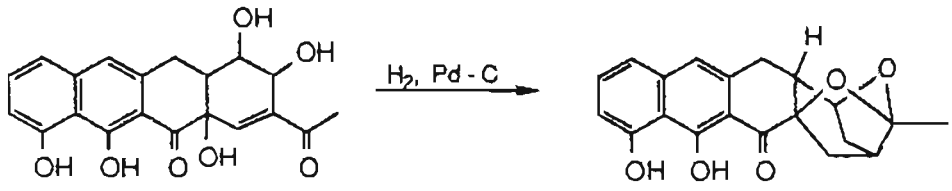
152: 1,2,3,4-tetrahydro-1-oxophenanthrene

Figure 2.5

the dihydroxynaphthalene structure. Careful acetylation of the aglycone revealed the presence of a tertiary hydroxyl functionality, which was undetected in prior work (Scheme 2.2).[72] Acetonide formation also established the presence of a *cis*-diol group. Hydrogenation of the double bond in the aglycone resulted in a net overall loss of two oxygen atoms to give pillaranone. NMR and IR studies of pillaranone indicated the absence of olefinic, hydroxyl, and ketone functionalities. Ultimately, an X-ray analysis of pillaranone unequivocally established the ketal structure **154** shown in Scheme 2.3.[75] Further NMR and IR studies permitted the assignment of structures **140a** and **140b** for pillaromycin and pillaromycinone.[74] X-ray analysis of pillaranone also permitted assignment of the absolute configuration of **140a**: 3(**S**), 4(**R**), 4a(**R**), 12a(**R**)-2-acetyl-3,4,4a,5,12,12a-hexahydro-12-oxo-3,4,10,11,12a-pentahydroxynaphthacene (**140a**)

Scheme 2.2 Asai's Degradations

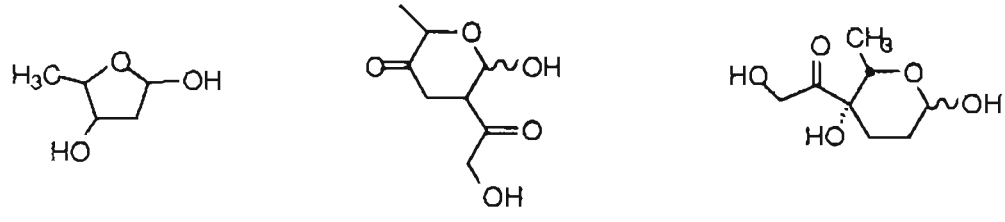




140a: Pillaromycinone **154:** Pillaranone

Scheme 2.3 Degradation of pillaromycinone

The structure of pillarose, originally proposed to be **157** by Shibata, *et al.*,[69] in 1964 (Figure 2.6), was radically revised to **158** by Asai and co-workers[77] in 1970. The new structure was found to consist of an aldohexose with a ketone and a hydroxyacetyl substituent. An X-ray analysis by Fraser-Reid and Clardy in 1975 led to the revised structure **159** where the hydroxyacetyl substituent are attached to the C-4 carbon.[78]

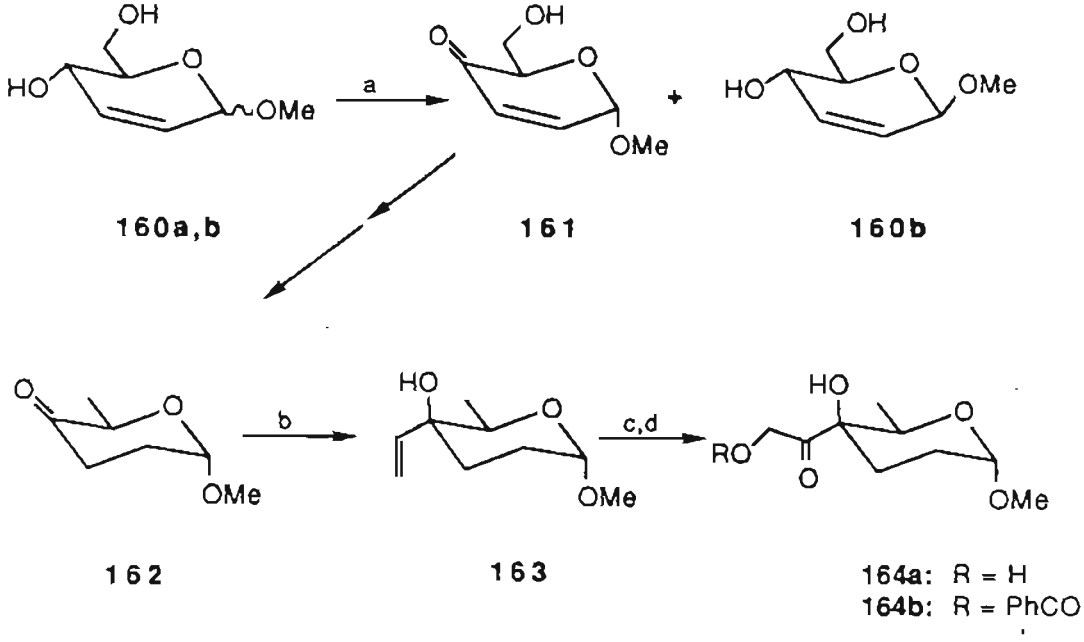


157: Shibata **158:** Asai **159:** Fraser-Reid

Figure 2.6 Proposed structures of pillarose

The structure of pillarose was unequivocally established by synthesis as shown in Scheme 2.4.[79] The ketone **162**, prepared from **160** by established procedures, was reacted with vinylmagnesium bromide to give the allyl alcohol **163**. Treatment of **163** with osmium tetraoxide and hydrogen peroxide gave the dihydroxyketone **164a** in 21% yield. Comparison of the NMR spectrum of the benzoylated product **164b** with an authentic sample of benzoylated pillarose showed they were identical.

Scheme 2.4 Fraser-Reid's Synthesis



a. MnO_2, CH_2Cl_2 b. C_2H_3MgBr, THF
c. OsO_4, t-BuOH, H_2O_2, d. PhCOCl

II. Synthetic Background

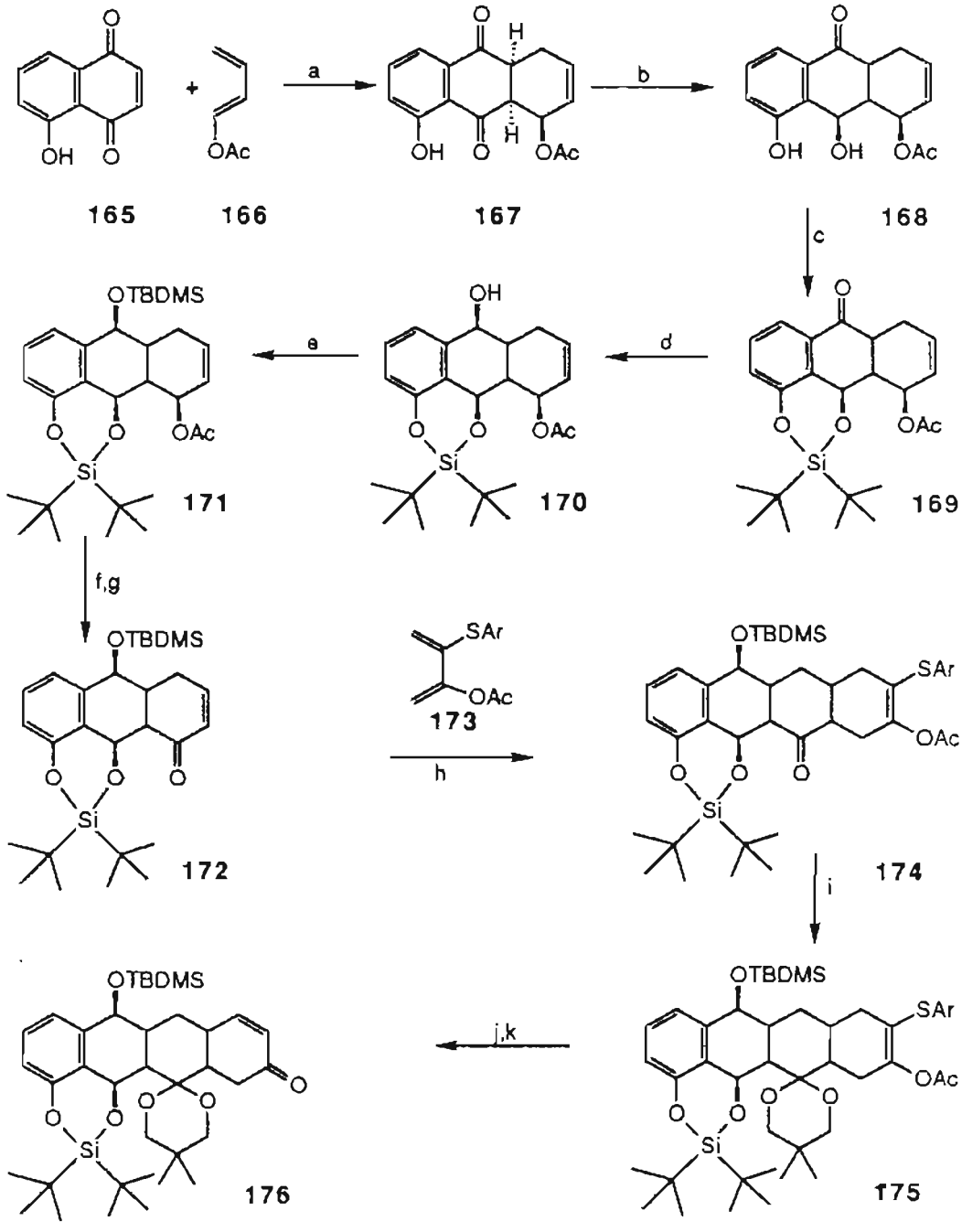
There have been two attempted syntheses of pillaromycinone. The first attempt, reported by Trost, *et al.*,[80] in 1982, furnished 12a-deoxy-pillaromycinone. A few years later (1986), White, *et al.*,[81] reported the synthesis of (+)-12a-deoxy-1,2-dihydropillaromycinone.

A. Trost's Approach

Trost utilized the linear approach shown in Schemes 2.5, 2.6, and 2.7.[80] Successive Diels-Alder cycloadditions were employed to transform the bicyclic quinone to a tricyclic quinone and then into a tetracyclic intermediate.

Lewis acid catalyzed Diels-Alder cycloaddition of jugalone (**165**) with 1-acetoxybutadiene yielded a greater than 20:1 ratio of tricyclic isomers in which **167** was the major product. Chemoselective reduction of the hydrogen-bonded quinone carbonyl with sodium borohydride gave **168**. Further manipulation required protection of the phenolic and hydroxyl functionalities in **168**. The required protecting group needed to be stable to acidic and basic conditions, yet removable in the presence of another silyl ether protecting group. This protection was achieved through treatment of **168** with di-*t*-butyldichlorosilane, which furnished the silylene protected **169** in 84% yield. The remaining carbonyl in **169** was reduced with lithium borohydride (59%) to the alcohol **170**.

Scheme 2.5 Trost's Synthesis

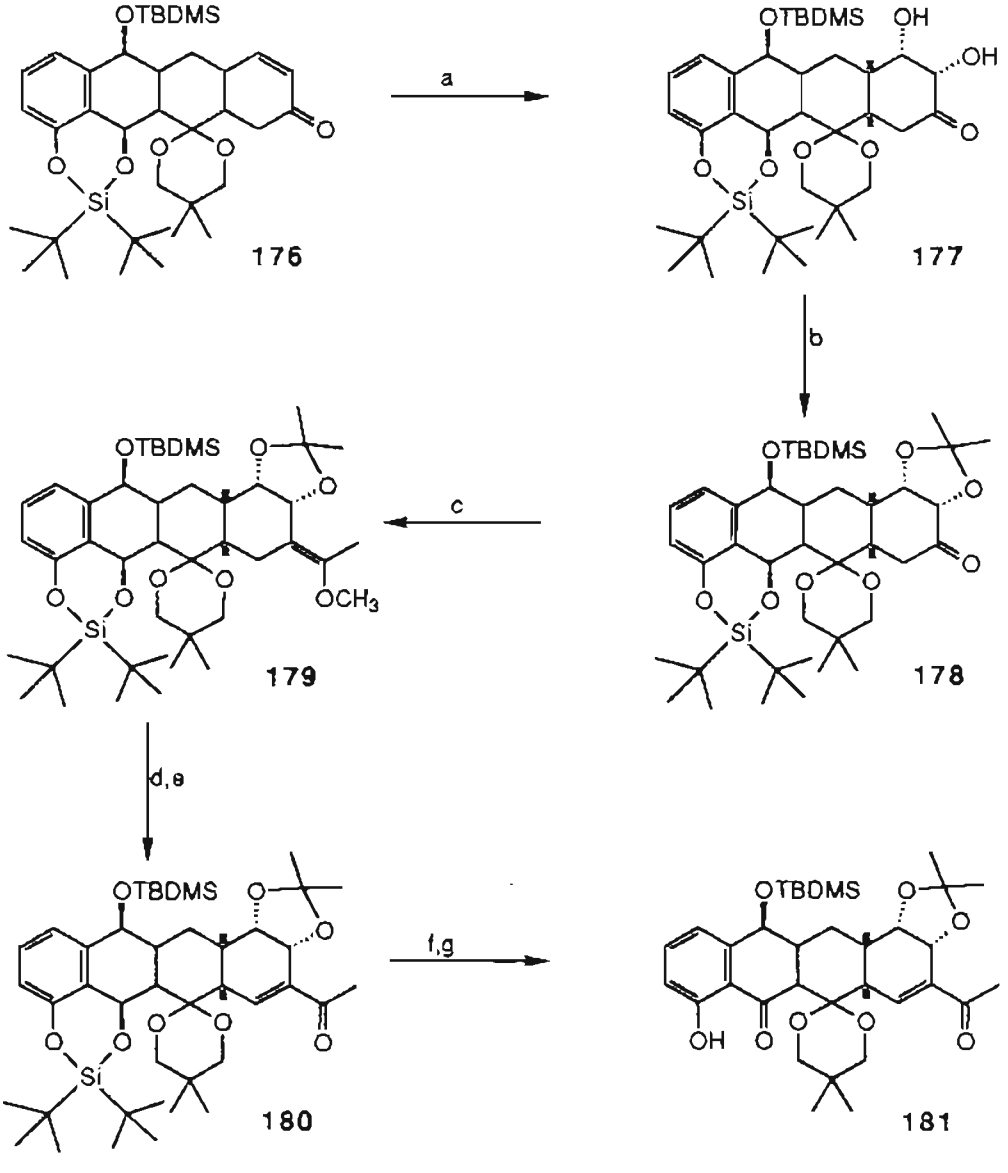


a. BF_3 Et_2O b. $NaBH_4$ c. t-Bu_2SiCl_2 d. $LiBH_4$ e. t-$BuMe_2SiCl$
f. Dibal-H g. Ac_2O, DMSO, Et_3N h. BCl_3 i. 2,2-Dimethyl-1,3-propanediol, camphorsulfonic acid j. $NaIO_4$ k. H^+

The reduction was conducted to only 50% conversion in order to prevent cleavage of the acetate. Protection of the resulting alcohol **170** by silylation with *t*-butyldimethylsilylchloride furnished **171** in 86% yield. Reductive cleavage of the acetate group in **171** with diisobutylaluminum hydride (91%), followed by oxidation of the resultant alcohol with acetic anhydride and dimethyl sulfoxide (82%), produced the enone **172**. Diels-Alder cycloaddition of **172** with 2-acetoxy-3-thiophenylbutadiene under boron trichloride catalysis gave the tetracyclic adduct **174** in 83% yield. The regiochemistry of **174** was assigned by analogy with the corresponding reaction of the diene with 2-cyclohexenone. Protection of the ketone was achieved through ketallization of **174** (75-80%) to **175**. Conversion of **175** to the unsaturated enone **176** was performed in two steps. Periodate oxidation of the sulfide **175** gave a sulfoxide intermediate, and acid cleavage of the enol acetate to a ketone was accompanied by elimination of phenylsulfenic acid to give the enone **176** in 60-74% overall yield.

As shown in Scheme 2.6, osmium tetraoxide hydroxylation of **176** produced the diol **177**, which was protected as the acetonide **178** (72% overall yield). Reaction of **178** with 1-methoxyethyltriphenylphosphorane at -100 ^{o}C gave the enol ether **179** (66%) as a 2:1 mixture of isomers. Singlet oxygen oxidation of **179** in the presence of methylene blue, followed by *in situ* reduction with triphenylphosphine, furnished the enone **180** in 78% yield. The silylene group in **180** was removed by treatment with pyridinium hydrofluoride (88%) and the resulting

Scheme 2.6 Trost's Synthesis



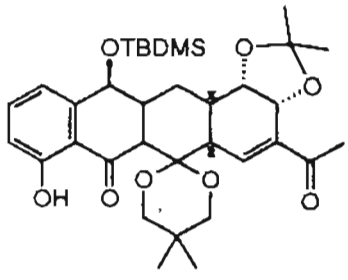
a. OsO_4, Py, THF b. 2,2-Dimethoxypropane c. $Ph_2P(O)=C(OCH_3)CH_3$
d. $^1O_2$ e. Ph_3P f. Pyridinium Hydrofluoride g. MnO_2

sensitive benzylic alcohol intermediate was oxidized with manganese dioxide to the ketone **181** in 76% yield.

Acetylation of the phenolic group in **181** (98%) gave the acetate **182a** and then desilylation with tetrabutylammonium fluoride and benzoic acid (97%) yielded the alcohol **182b** (Scheme 2.7). Mesylation of **182b** to **182c**, followed by treatment with tetrabutylammonium oxalate and DBU gave a C-ring aromatized product, which was acetylated to **183**. Final deblocking involved removal of the acetonide with camphorsulfonic acid and then acetylation to **184**. Hydrolysis of the enol ether with aqueous acetic acid in the presence of N-bromosuccinimide and subsequent acetylation gave the pentaacetate **185** as yellow crystals. The deacetylated product was unstable and could not be isolated. Comparison of the ^{1}H-NMR spectrum of **185** with that of the tetraacetate of authentic pillaromycinone revealed a surprisingly good match. High resolution mass spectroscopy gave an intense molecular ion peak at mass 564.1633 as compared to the calculated value of 564.1631.

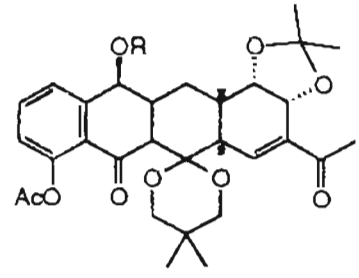
Trost's synthesis was straightforward; however, the linear approach was rather lengthy. Trost's utilization of successive Diels-Alder cycloadditions to fabricate a functionalized tetracyclic compound is noteworthy. The deacetylated product was unstable, due to the absence of a 12a-hydroxyl group, and readily underwent aromatization of the A ring. This instability prevented introduction of the 12a-hydroxyl group. Of particular interest was the development of the silylene protecting group and its stability and deprotection in the presence of other silyl groups.

Scheme 2.7 Trost's Synthesis



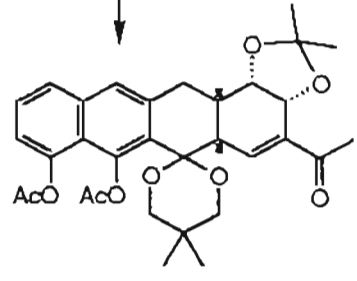
181

a,b,c



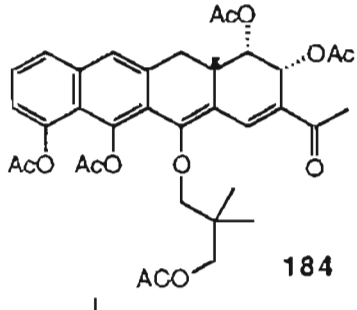
182a: R = TBDMS
182b: R = H
182c: R = Ms

d,e



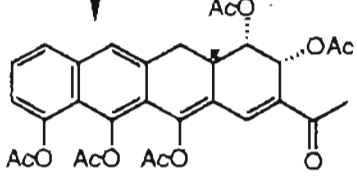
183

f,g



184

h,i



185

a. Ac_2O b. $PhCO_2H$, n-Bu_4NF c. MsCl
d. n-Bu_4N oxalate, lutidine e. Ac_2O
f. Camphorsulfonic acid g. Ac_2O
h. NBS, AcOH, H_2O i. Ac_2O

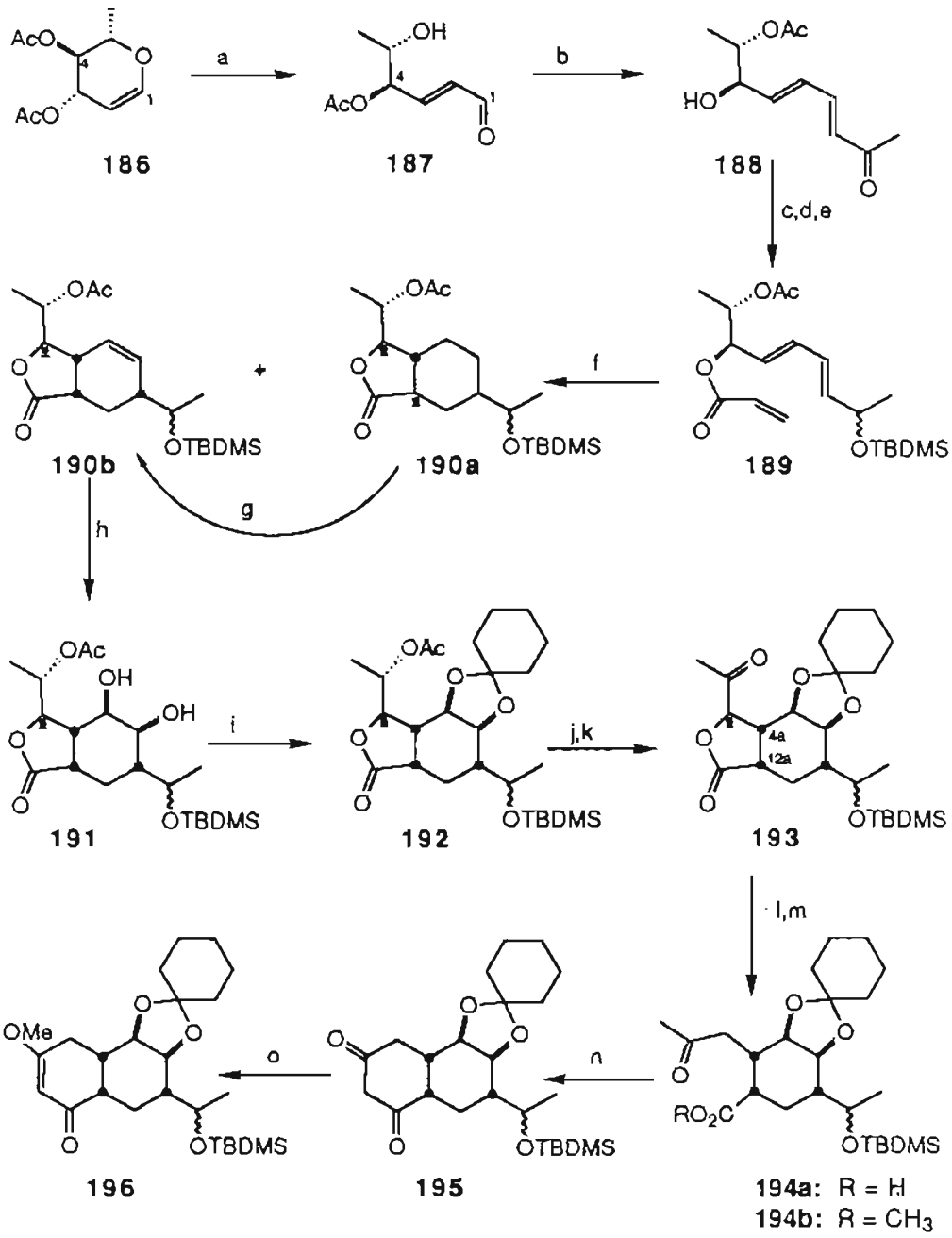
B. White's Approach

White's approach to pillaromycinone, shown in Schemes 2.8 and 2.9, elegantly employed L-rhamnose to elaborate the A ring with the correct absolute stereochemistry.[81] Intramolecular Diels-Alder cycloaddition was utilized to fabricate the chiral A ring through transfer of chirality from L-rhamnose. Further elaboration gave an AB ring unit which when condensed with a D ring subunit led to concomitant formation of the C ring.

L-rhamnal **186**, prepared in three steps from L-rhamnose, was transformed into the E-hexenal **187** *via* a Perlin transformation (93%). Wittig reaction of **187** gave a 2:1 E,Z mixture (88%) in which the E-isomer **188** was the major product. Acylation of **188** with acryloyl chloride, followed by reduction of the ketone and silylation of the resultant alcohol furnished the silyl ester **189** as an epimeric mixture in 53% overall yield.

Intramolecular Diels-Alder cycloaddition of **189** (70%) yielded a 2.5:2.5:1 mixture of products in which **190a** and **190b** were the major isomers. The *trans*-fused isomer **190a** was isomerized to the more stable *cis* isomer **190b** by treatment with lithium diisopropyl amide (LDA). Hydroxylation of **190b** with osmium tetraoxide proceeded stereospecifically on the convex face and gave the diol **191**, which was protected as its cyclohexylidene derivative **192** in 65% overall yield. Saponification of the acetate in **192** and oxidation of the resultant alcohol furnished the ketone **193** (61%). Reductive cleavage of the lactone in **193** with samarium diiodide

Scheme 2.8 White's Synthesis



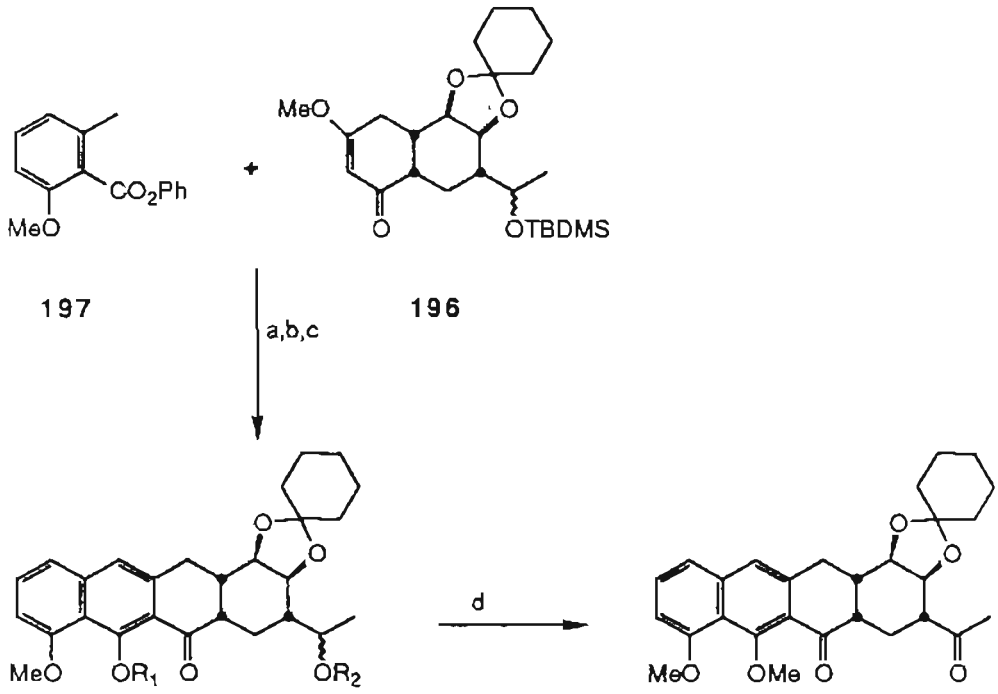
a. $HgSO_4$, H_2SO_4, dioxane, acetone b. $Ph_3P{=}CHCOCH_3$ c. $CH_2{=}CHCOCl$
d. $NABH_4$, $CeCl_3$, MeOH e. t-$BuMe_2SiCl$, lutidine f. toluene, 210°C g. LDA
h. OsO_4, TMNO, THF, H_2O i. $(MeO)_2C(CH_2)_5$, H^+ j. K_2CO_3, MeOH
k. PCC l. SmI_2, $FeCl_3$ m. CH_2N_2 n. $KOBu^t$ o. CH_2N_2

gave the keto acid **194a**, which was esterified with diazomethane to **194b** in 84% overall yield. Intramolecular Claisen condensation of **194b** produced the dione **195**. Reaction of **195** with diazomethane gave a 2.5:1 mixture of enol ethers (89% from **194b**), in which **196** was the major product.

Condensation of **196** with the anion of **197** in the presence of cerium trichloride furnished the naphthacenone **198a** in 62% yield (Scheme 2.9). The presence of cerium (III) was crucial to the success of the reaction for in its absence, the reaction proceeded in poor yield. Methylation of the phenolic group in **198a** followed by cleavage of the silyl protective group in **198b** gave **198c**. Oxidation of **198c** furnished the protected deoxy-dihydropillaromycinone **199** in 70% overall yield.

Although White's approach did not yield pillaromycinone, it was much shorter than Trost's route. Furthermore, it had the added feature of utilizing the chirality of L-rhamnose to form an optically active product. An interesting feature of the transfer of chirality from L-rhamnose to the final product was that the chiral center at the C-3 acetate carbon in **186** was used to generate the chiral ester **189**. Upon Diels-Alder cycloaddition, two formerly achiral olefinic carbons became new chiral bridging centers in **190a,b** at what was to be C-4a and C-12a in the final product. The chiral center at C-4a was to ultimately determine the stereochemistry of the other bridging carbon during the transformation of **190a** to **190b**, as well as the diol centers. White's approach suffered from the inability to regiospecifically and stereochemically introduce the 12a-hydroxyl group and the C-1,2 double bond.

Scheme 2.9 White's Synthesis



198a: R_1 = H R_2 = TBDMS
198b: R_1 = Me R_2 = TBDMS
198c: R_1 = Me R_2 = H

199

a. LDA, $CeCl_3$, THF b. Me_2SO_4, K_2CO_3 c. *n*-Bu_4NF d. PCC

III. Synthesis

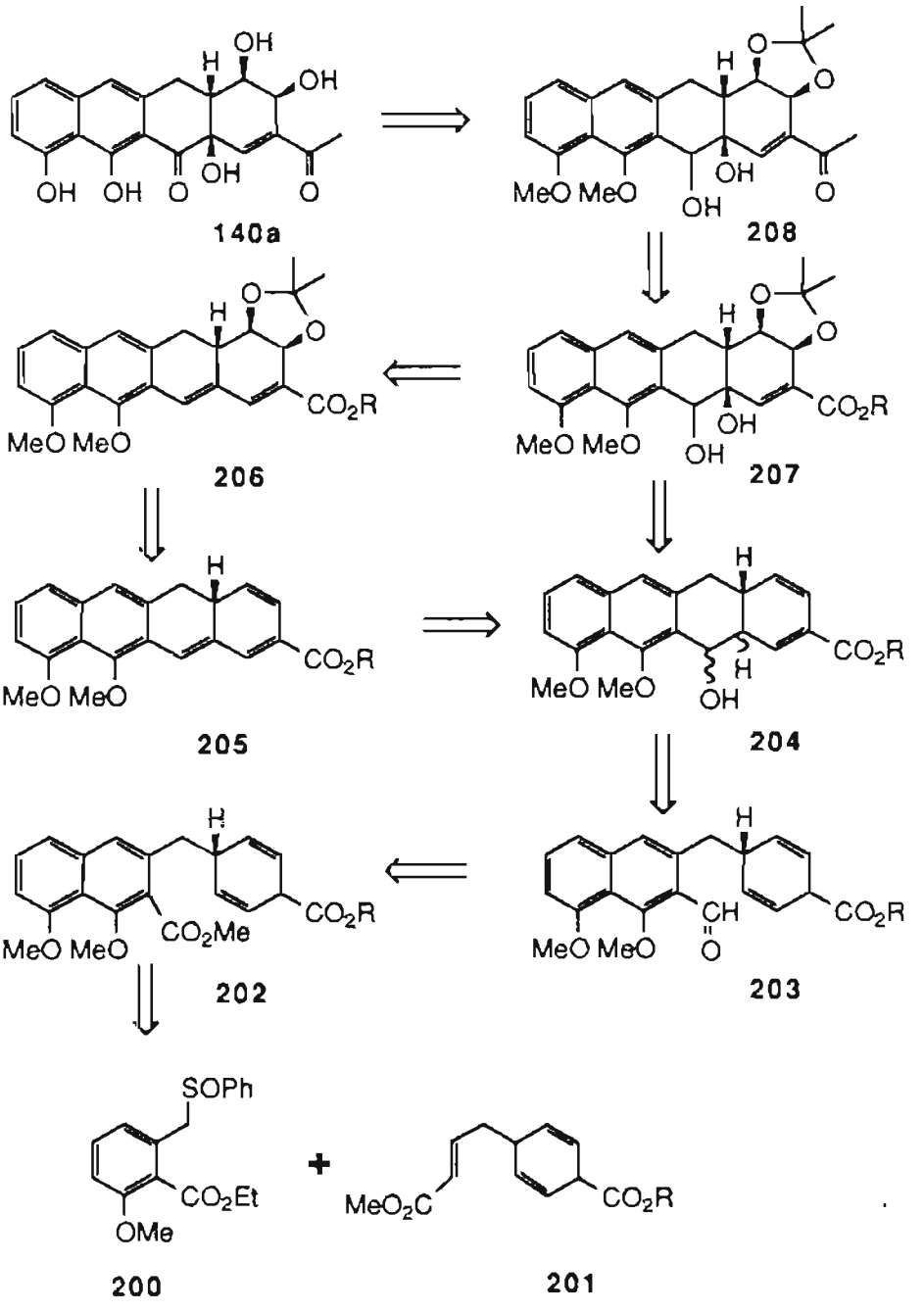
A. First Approach

The first approach examined for synthesis of pillaromycinone was based upon the retrosynthetic analysis shown in Scheme 2.10. A key element of this route was fabrication of the naphthalene **202** through condensation of the sulfoxide **200** with the unsaturated ester **201**. Another key element was fabrication of the tetracyclic intermediate **204** through intramolecular ene reaction of the aldehyde and olefinic moieties in the naphthalene intermediate **203**.

Introduction of subsequent groups would be accomplished through selective manipulation of the olefinic and carboxyl functionalities in **205** (Scheme 2.10). The problem encountered previously by Trost and White in their inability to introduce the C-12a hydroxy group would be addressed through *cis*-hydroxylation of the B-ring double bond in **206** to give the diol **207**. Furthermore, the presence of the A-ring double bond in **207** would eliminate the problem of its introduction experienced by White.

Selective *cis*-hydroxylation[82] of the isolated double bond in **205** would be followed by protection of the resulting diol to give **206**. Subsequent *cis* hydroxylation of the B-ring double bond would give diol **207**. Conversion of the carboxylate group in **207** to an acetyl functionality would give **208**.[83] Finally, selective oxidation[84] of the benzylic hydroxyl in **208**, followed by deprotection of the diol and phenolic functionalities would generate

Scheme 2.10 Retrosynthetic analysis

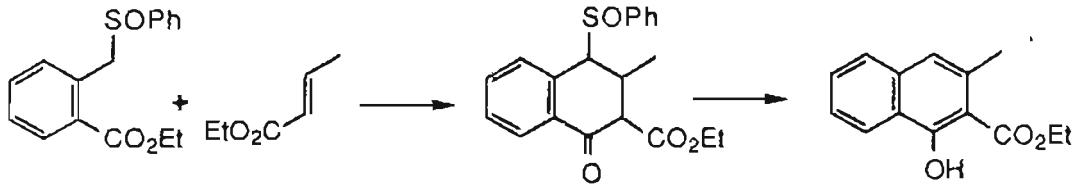


pillaromycinone. The *trans*-substituted cyclohexadiene moiety in **201** would be derived through Birch reduction[85] of a 4-substituted benzoic acid.

Control of stereochemistry is essential for successful synthesis of complex molecules and the proposed route addresses this point. Ene reaction of **203** would initially give the hydroxy intermediate **204**, which on dehydration would give the triene **205**. Examination of molecular models indicated that, although nearly planar, **205** would be slightly convex due to the sp^3 center at C-4a. Osmium tetraoxide hydroxylation of both **205** and **206** was anticipated to occur from the convex face to give the *cis* diols **206** and **207** with the desired stereochemistry. However, the question remaining is: To what extent would the hydroxylation reaction be streoselective?

Construction of the naphthalene **202** was based upon the annelation methodology developed earlier by Hauser and Rhee.[54] As shown in Scheme 2.11, these investigators had reported that the anion of ethyl 2-carboxy-benzyl phenyl sulfoxide **209** undergoes condensation with Michael acceptors, such as ethyl crotonate (**210**), to give the tetralone intermediate **211**. Thermal elimination of phenyl sulfenic acid aromatizes the newly formed ring furnishing ethyl 1-hydroxy-3-methyl-2-naphthalene-carboxylate (**212**).

Scheme 2.11

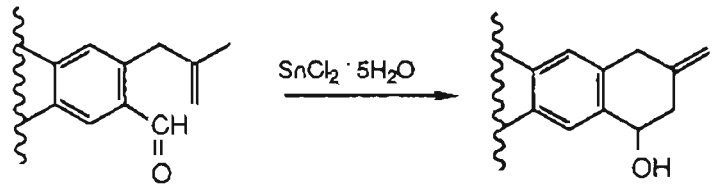


209 **210** **211** **212**

1. Ene Reaction

The proposed use of an ene reaction for fabrication of the tetracyclic intermediate **214** from the naphthalene **213** (Scheme 2.10) was based upon the similar chemistry reported by Hauser and Mal in a synthesis of γ-citromycinone (Scheme 2.12).[86]

Scheme 2.12



213 **214**

The ene reaction, shown in equation 2.1, is a thermally allowed condensation of an alkene having an allylic hydrogen (ene) with a compound containing a double or triple bond (enophile).[87] The reaction is formally a concerted process forming a new bond with migration of the double bond and a 1,5-hydrogen shift. The ene reaction is mechanistically related to the well know Diels-Alder reaction since both can proceed through a cyclic transition state involving six electrons. Unlike the Diels-Alder reaction where two new carbon-carbon bonds are formed, the ene reaction involves the breaking of a carbon-hydrogen bond as well as the formation of one carbon-carbon bond. This results in a much higher

energy of activation for the ene reaction than for the Diels-Alder reaction and therefore higher temperatures are required for the reaction to occur. This has greatly limited the synthetic use of this reaction. While it has been demonstrated that some thermal ene reactions are concerted, others clearly proceed through a stepwise mechanism.

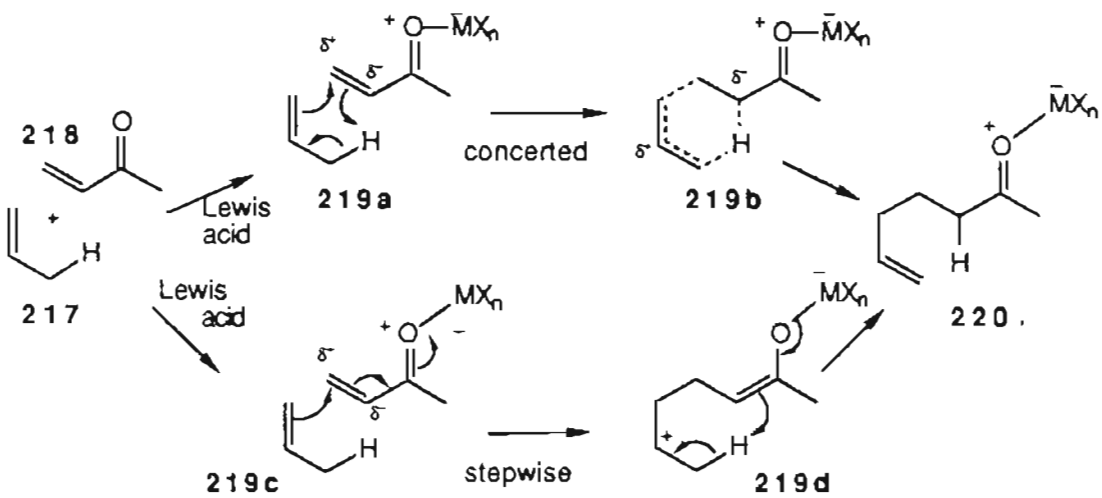
Equation 2.1

215 **216**

Concerted ene reaction mechanism

In contrast to the thermal reaction, the catalysed ene reaction proceeds under much milder conditons. As shown in Scheme 2.13, Lewis acid catalyzed ene reaction of the olefin **217** with activated enophiles **218** can proceed either through a stepwise mechanism with a zwitterionic

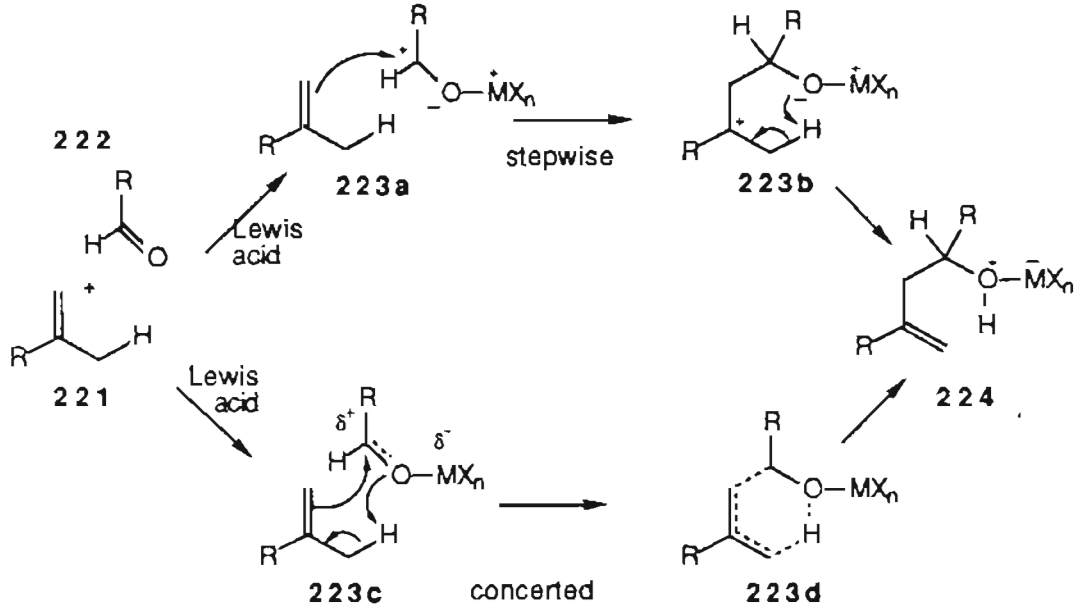
Scheme 2.13 Mechanisms of catalyzed ene reactions



intermediate or in a concerted manner with a polar transition state. The two mechanisms are similar and the particular mechanism depends on the ene, enophile, and catalyst.

Aldehydes have also been used extensively as enophiles in Lewis acid catalyzed ene reactions and the intramolecular ene reactions of unsaturated aldehydes has been extensively studied. These reactions can also proceed through either a stepwise or concerted mechanism as shown in Scheme 2.14. The stepwise mechanism requires prior activation of the aldehyde **222** by complexation with a Lewis acid which forms a carbenium ion at the carbonyl carbon in **223a**. Reaction of the ionic complex with the ene component results in bond formation and generation of a new carbenium ion center in **223b**. Subsequent transfer of the hydrogen to the oxygen

Scheme 2.14 Ene reaction with carbonyl enophiles



results in formation of a new double bond and an alcohol group. The concerted mechanism proceeds through the polar transition state **223d** with the Lewis acid complexed carbonyl reacting with the ene component. Although some mechanistic information can be obtained from isotope effects or analysis of product mixtures, attempts to distinguish the two mechanisms are difficult. A general rule is that the more reactive the ene or enophile-Lewis acid complex is in ene reaction, the more likely the reaction is to be stepwise. Present evidence suggests that most reactions with activated enophiles are concerted while those with carbonyl compounds are stepwise.

Whether the mechanism is concerted or stepwise, considerable positive charge develops on the central carbon of the ene component in the Lewis acid catalyzed reaction. For this reason, 1,1-disubstituted alkenes, being better able to stabilize a positive charge, are most reactive. In this respect, Lewis acid catalyzed ene reactions differ from thermal ene reactions where steric effects are more important. In general, the order of reactivity for alkenes in Lewis acid catalyzed reactions is as shown in Figure 2.7. The 1,1-disubstituted alkene **266a** is the most reactive because the disubstituted vinylic carbon is better able to stabilize a positive charge and the unsubstituted vinylic carbon is sterically more accessible for reaction.

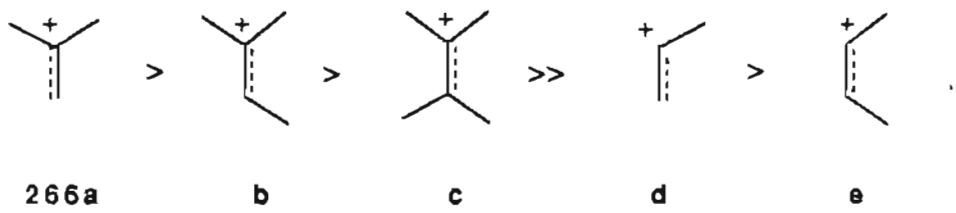


Figure 2.7 Order of alkene reactivity

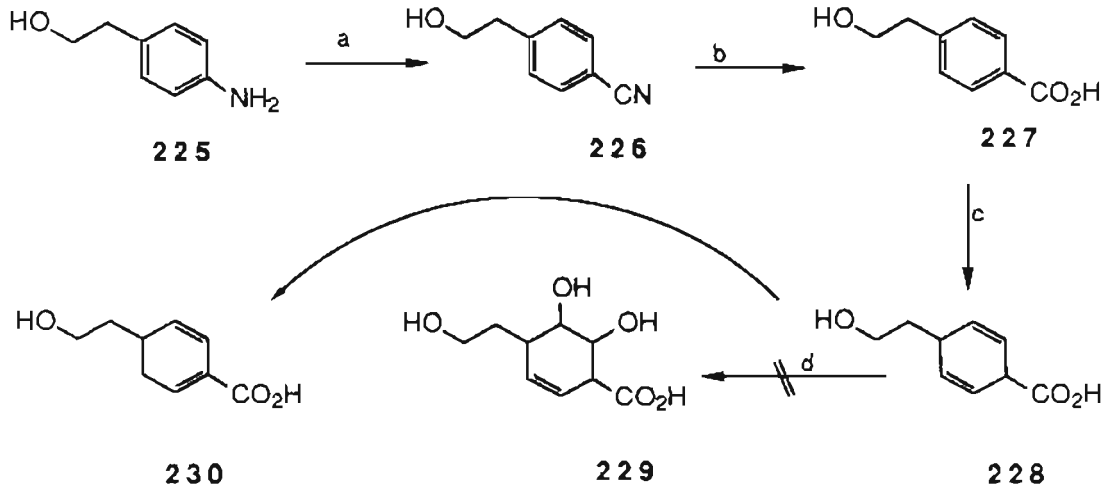
The 1,2-disubstitued alkene **266e** is the least reactive due to the fact that the mono substituted vinylic carbon is not as able to support a positive charge and substitution at the other vinylic carbon further sterically hinders the reaction.

Side reactions are also more prevalent in Lewis acid catalyzed ene reactions with monosubstitued and disubstituted olefins (**266d,e**). Furthermore the steric accessibility of the hydrogen that is to be abstracted is an important consideration. Methyl and methylene hydrogens are removed much more easily than methine hydrogens. The relative ease of abstraction of the methyl or methylene hydrogen depends on the enophile and the mechanism. With formaldehyde, for example, methylene hydrogens are abstracted more easily.

2. Synthesis

The route shown in Scheme 2.15 was undertaken for the synthesis of the cyclohexadienyl Michael acceptor **201**. Diazotization of 4-(2-hydroxyethyl)aniline (**225**) with sodium nitrite followed by treatment with copper(I) cyanide[88] furnished the nitrile **226** (33%). Hydrolysis of **226** with potassium hydroxide and hydrogen peroxide[89] gave the benzoic acid **227** in 56% yield. Birch reduction[85] of **227** was accomplished with lithium in liquid ammonia containing a small amount of ethanol. The initial deep blue solution faded after 10-15 minutes, and workup gave 4-(2-hydroxyethyl)-2,5-cyclohexadiene carboxylic acid (**228**) as a 1:1 mixture of *cis* and *trans* isomers in 86% yield.

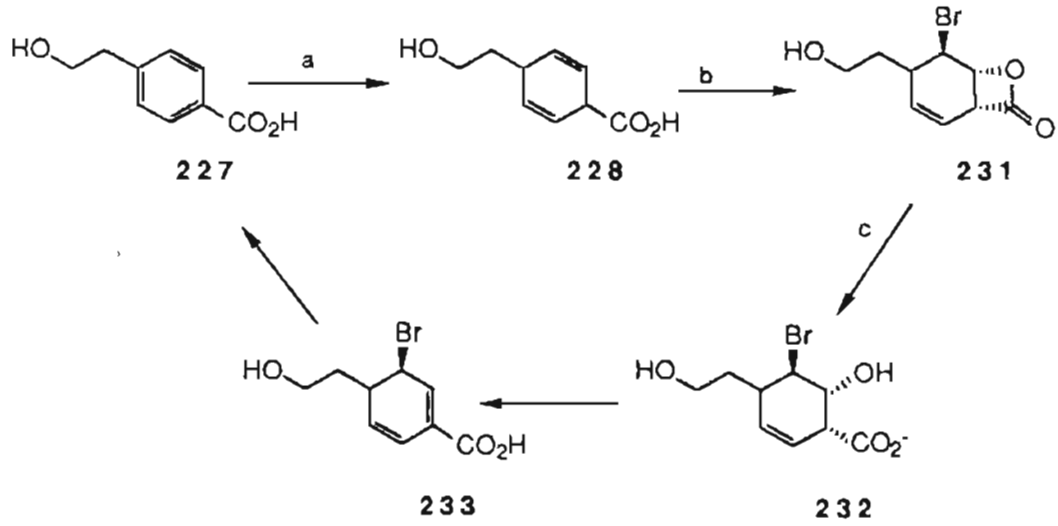
Scheme 2.15



a. HCl, $NaNO_2$, Na_2CO_3, CuCN b. KOH, H_2O_2, EtOH
c. Li, EtOH, NH_3(liq) d. OsO_4, TMNO, acetone, H_2O

The diene proved to be unstable and underwent both isomerization and aromatization. Since the diene was unstable, functionalization of the ring was undertaken in an attempt to convert it to a more stable product. Attempted hydroxylation of one of the double bonds with osmium tetraoxide[82] yielded a complex mixture of products. Conversion of **228** to the lactone **231** was undertaken as shown in Scheme 2.16. Treatment of an aqueous bicarbonate solution of the diene **228** with a methylene chloride solution of bromine[90] gave the lactone **231**, but in only 30% yield. The lactone proved to be stable to acid hydrolysis, but could be hydrolyzed with aqueous bicarbonate to the salt **232**. However, upon neutralization and work up, **232** yielded predominantly the conjugated diene **233** resulting from dehydration of the β-hydroxy acid intermediate.[91]

Scheme 2.16

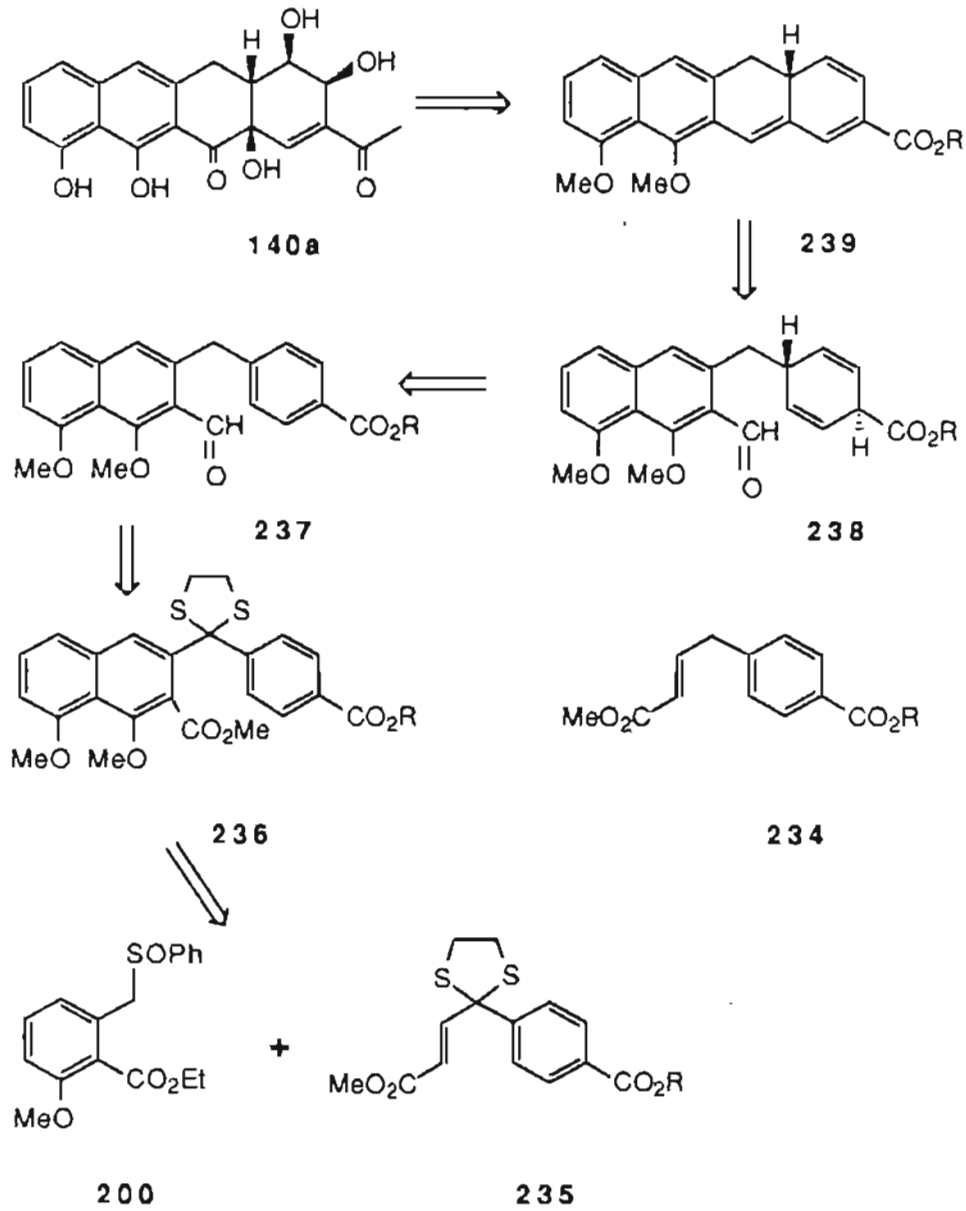


a. Li, EtOH. NH_3 (liq) b. (1) $NaHCO_3$, H_2O, (2) Br_2, CH_2Cl_2 c. $NaHCO_3$, H_2O, THF

B. Second Approach

The instability of the dihydrobenzoic acid led to the modified strategy shown in Scheme 2.17 in which the diene would be generated immediately before ene reaction. Since electron-deficient rings undergo Birch reduction much more rapidly than electron-rich rings,[92] it was anticipated that **237** would undergo selective reduction to **238**. Ene reaction of **238** and *cis*-hydroxylation of the triene **239** were to be accomplished as described previously. Since the benzylic protons in the ester **234** are very acidic, it would be necessary to block this position in order to prevent isomerization of the double bond during the Michael condensation. This would be accomplished through protection of the benzylic position as the

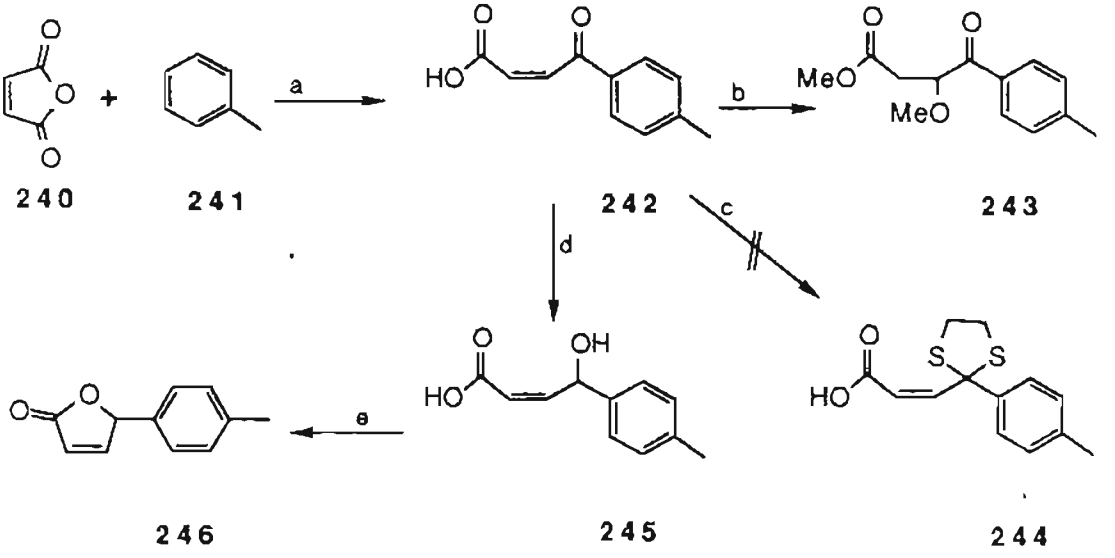
Scheme 2.17 Retrosynthetic analysis



dithioketal **235**.[93] In further steps, the dithioketal would be converted into a methylene functionality through hydrogenolysis[94] of **236** to give **237**.

Synthesis of the Michael acceptor **235** was undertaken as shown in Scheme 2.18. Friedel-Crafts[95] acylation of toluene with maleic anhydride (**240**) using aluminum chloride gave the aroyl acrylic acid **242** in 41% yield. Attempted esterification with methanol and sulfuric acid yielded the methoxy substituted methyl ester **243**, resulting from conjugate addition of methanol to the double bond. The ^{1}H-NMR spectrum showed two methoxy singlets at 3.47 and 3.79 ppm (δ) and the absence of any vinylic resonances. Attempts to prepare the thioketal **244** from **242** were unsuccessful.[93] A ^{1}H-NMR spectrum of the product showed the absence of vinylic hydrogens and apparently as with methanol, the thiol group also had added preferentially to the double bond instead of the carbonyl group.

Scheme 2.18

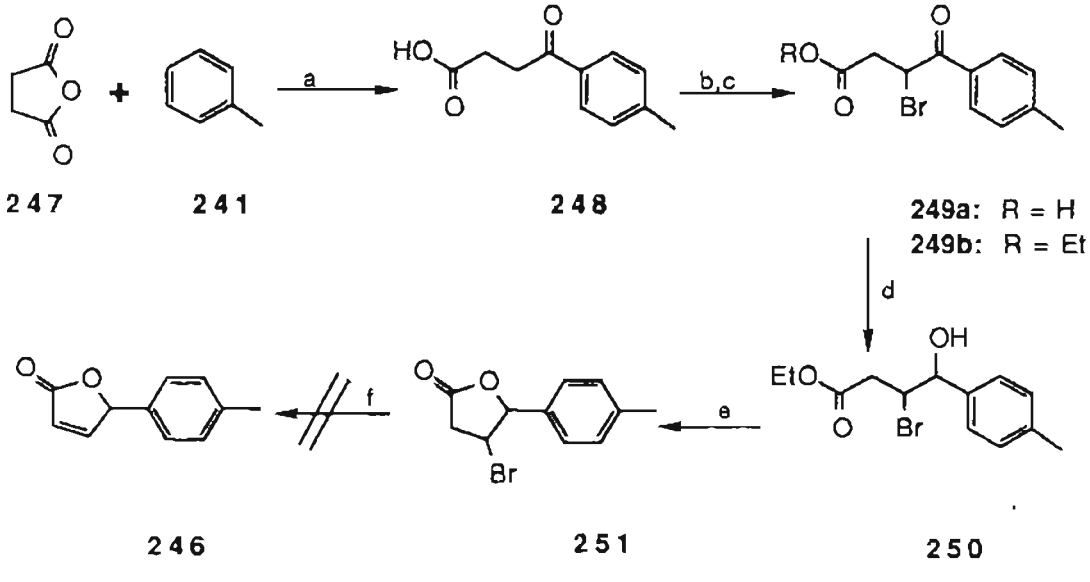


a. $AlCl_3$, nitrobenzene, CH_2Cl_2 b. H_2SO_4, MeOH c. $HSCH_2CH_2SH$, $BF_3 \cdot Et_2O$, CH_2Cl_2
d. $NaBH_4$, NaOH, H_2O e. H^+, Et_2O or CH_2Cl_2

The suitability of the unsaturated lactone **246** as a Michael acceptor was investigated next[96]. Reduction of the ketone carbonyl in **242** with sodium borohydride in aqueous sodium hydroxide solution gave the unsaturated hydroxy acid **245** in 80% yield. However, attempted lactonization of **245** under a variety of acidic conditions[97] gave only a low yield of the desired lactone **246**.

The alternative preparation of **246** where the lactone is generated first and unsaturation subsequently introduced, is shown in Scheme 2.19. Friedel-Crafts acylation[95] of toluene with succinic anhydride (**247**) gave **248** in 66% yield. Bromination of **248** with cupric bromide[98] furnished the bromoketone **249a** which was esterified to **249b**. Sodium borohydride

Scheme 2.19



a. $AlCl_3$, nitrobenzene b. $CuBr_2$, $CHCl_3$, c. H_2SO_4, MeOH
d. $NaBH_4$, MeOH e. TsOH, benzene f. DBU, benzene

reduction of **249b** gave the hydroxy bromo ester **250** in good yield. Lactonization with toluenesulfonic acid in benzene produced the lactone **251**. However, repeated attempts to dehydrohalogenate **251** to **246** with DBU[99] failed.

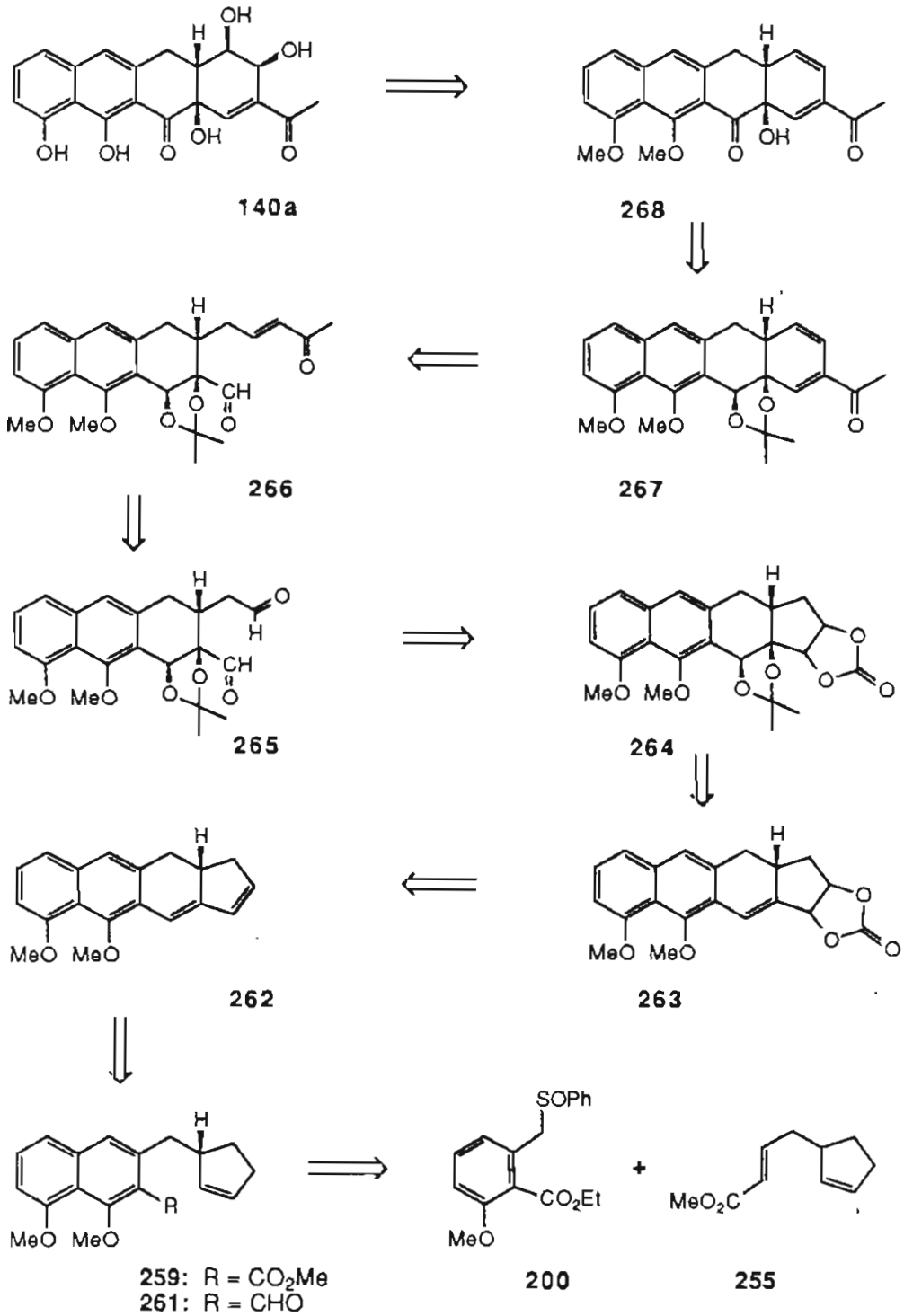
The inability to generate the cyclohexadiene Michael acceptor **201** or the dithioketal Michael accepter **235** led us to examine other possible Michael acceptors.

C. Third Approach

An approach to pillaromycinone utilizing the cyclopentenyl Michael acceptor **255** is shown in Scheme 2.20. The olefin in the cyclopentene ring should be stable to isomerization and yet it was anticipated that it should participate in the ene reaction. Although this approach was flexible in allowing the use of either a 5-membered or 6-membered ring, the Michael acceptor with the 5-membered ring was examined first. Since ring systems containing a 5-membered ring fused to a 6-membered ring are more stable in the *cis* form, this property was to be utilized to ensure that hydroxylation of **263** would give the *cis*-fused product **264**.

Condensation of the sulfoxide **200** with the Michael acceptor **255**[54] would upon methylation give the ester **259**, which would then be transformed to the aldehyde **261**. Ene reaction[82] of **261** and dehydration of the alcohol intermediate would give the tetracyclic unsaturated product **262** possessing fused six and five-membered rings. Preferential hydroxylation[82] of the less conjugated and less substituted olefin in the five-membered

Scheme 2.20 Retrosynthetic analysis



140a **268**

266 **267**

265 **264**

262 **263**

259: R = CO_2Me
261: R = CHO

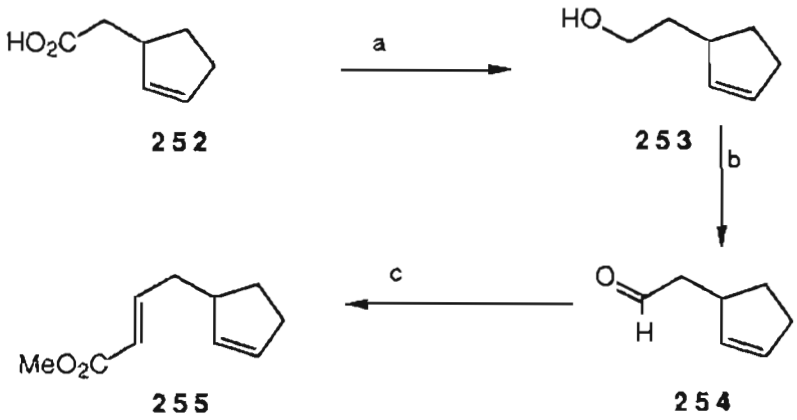
200 **255**

ring followed by protection of the diol as a carbonate ester would give **263**. Subsequent *cis*-hydroxylation of the remaining double bond, followed by protection of the diol as an acetonide would give **264** with the required *cis* configuration. Ring expansion of the 5-membered ring to a 6-membered ring would be accomplished by hydrolysis of the carbonate and oxidative cleavage of the resultant diol[100] to the dialdehyde **265**.

Since the Wittig[101] reaction is sensitive to steric factors, conversion of the less hindered aldehyde in **265** to the unsaturated ketone **266** was anticipated. Intramolecular aldol cyclization[66] of **266**, followed by dehydration would give the diene **267**. Hydrolysis of the acetonide and oxidation of the benzylic hydroxyl functionality in **267** would give the ketone **268**. *Cis*-hydroxylation of the isolated double bond would occur from the convex face and demethylation of the aromatic phenolic groups would give pillaromycinone **140a**. The critical steps in this approach are the ene reaction, selective Wittig reaction, and the stereospecific hydroxylation of **263**. Based on the literature precedents, it was anticipated that these reactions should work.

Synthesis of the Michael acceptor **255** was accomplished as shown in Scheme 2.21. Reduction of cyclopenteneacetic acid **252** with lithium aluminum hydride furnished the alcohol **253** in 92% yield. Swern[65] oxidation of **253** gave the aldehyde **254** (90%). Because of its extremely unpleasant odor, **254** was not purified, but directly treated with the anion of trimethylphosphonoacetate[102] to provide the unsaturated ester **255** in 64% yield.

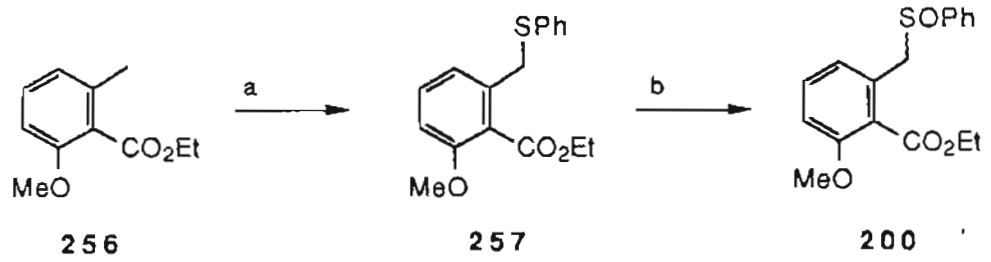
Scheme 2.21



a. LAH, Et_2O b. $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2 c. $(MeO)_2P(O)CH_2CO_2Me$, NaH, THF

The required sulfoxide **200** was prepared from ethyl 2-methyl-6-methoxybenzoate (**256**) as shown in Scheme 2.22.[103] Condensation of the anion of **256** with diphenyl disulfide gave the crude sulfide **257**. Sodium periodate oxidation followed by chromatography furnished the sulfoxide **200** in 57% overall yield.

Scheme 2.22

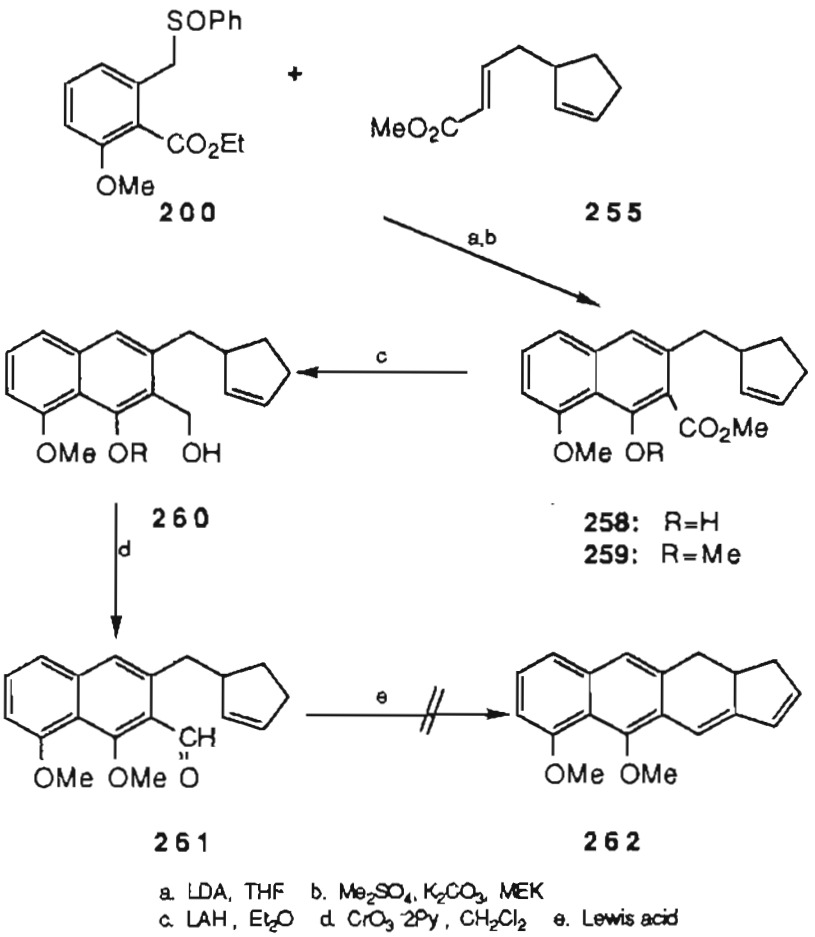


256 **257** **200**

a. LDA, PhSSPh, THF b. $NaIO_4$, MeOH

Michael addition of the anion of the sulfoxide **200** with the acceptor **255** was performed as shown in Scheme 2.23.[54] The orange anion of the sulfoxide **200**, generated with lithium diisopropylamide was reacted with the acceptor **255**, and upon thermal elimination of phenyl sulfenic acid gave the naphthalene **258** in 30-45% yield. After considerable study it was found that the yield could be improved to 45-55% through addition of copper(I) cyanide to the sulfoxide anion.

Scheme 2.23

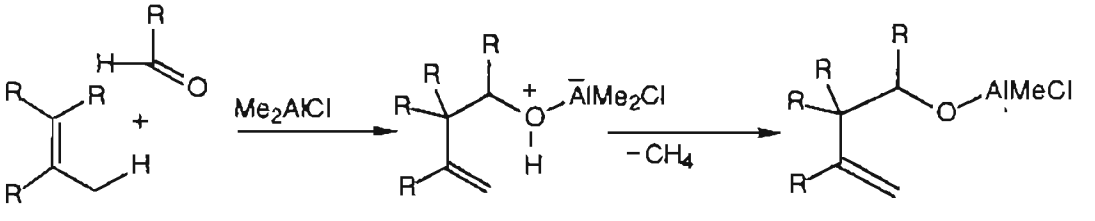


Methylation of **258** with dimethyl sulfate gave the methyl ether **259** (95%). Reduction of the ester group in **259** with lithium aluminum hydride furnished the alcohol **260**, which was oxidized with Collins[62] reagent to the aldehyde **261** in 77% overall yield.

Attempted ring closure of **261** to **262** utilizing the ene reaction proved to be disappointing. Treatment of the aldehyde **261** with the mild Lewis acid stannic chloride pentahydrate under the same conditions used in the citromycinone synthesis did not give any product.[86] A number of Lewis acids were investigated; however, none gave the desired product. Anhydrous stannic chloride and titanium tetraisopropoxide gave no reaction while use of titanium tetrachloride, boron trifluoride, and ferric chloride gave intractable products.

Snider has reported that dimethylaluminum chloride is the reagent of choice for the catalyzed ene reaction.[104] This is based on the finding, as shown in Scheme 2.24, that once the ene reaction has taken place, the resulting Lewis acid-complexed alcohol **264** eliminates methane to yield the

Scheme 2.24 Dimethylaluminum Chloride Catalysis



263 **264** **265**

stable aluminum alkoxide **265**. This prevents subsequent proton catalyzed rearrangements and solvolysis. Despite its advantages, use of dimethyl- or diethylaluminum chloride as catalysts in the ene reaction of **261** did not yield any product.

Despite the expected lower reactivity of 1,2-disubstitued alkenes in ene reactions, the total lack of reactivity encountered with the cyclopentene olefin is surprising. It is possible that the observed lack of reactivity could arise from constraint of the alkene to a cyclic five-membered system.

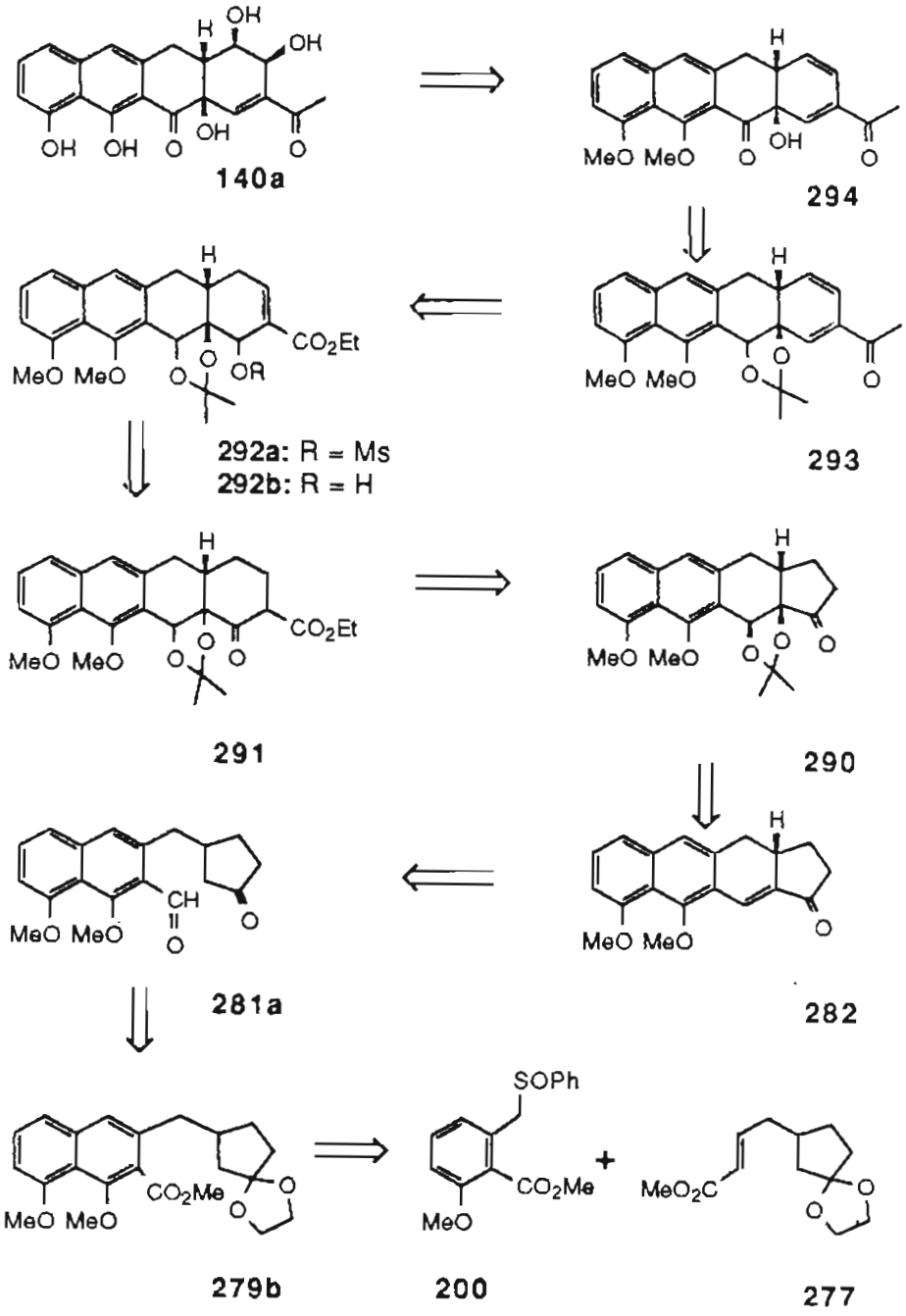
In summary, while synthesis of the ene substrate **261** was successfully achieved, ring closure of **261** to **262** proved to be an insurmountable obstacle. The intramolecular ene reaction is a useful ring forming method; however, its use here for synthesis of pillaromycinone was precluded.

D. Fourth Approach

The previous sections have described various approaches to tetracyclic intermediates to pillaromycinone based on the use of the ene reaction. An alternate approach utilizing aldol cyclization is shown in Scheme 2.25. The key step would be cyclization of the keto aldehyde **281a** to give the unsaturated ketone **282**. The keto aldehyde **281a** would be derived from **279b** through reduction of the carbomethoxy group in **279b** to an aldehyde and hydrolysis of the ketal protecting group. The naphthalene **279b** would in turn be derived through Michael condensation of the sulfoxide **200** with the acceptor **277**.[54] As noted previously, the presence of the five-membered ring would ensure that hydroxylation of the olefin in **282**, and protection of the resultant diol, would give the *cis*-fused product **290**. Ring expansion of **290** with ethyl diazoacetate[105] would give **291** with the 2-carboethoxy substituted six-membered A-ring *cis*-fused to the B-ring.

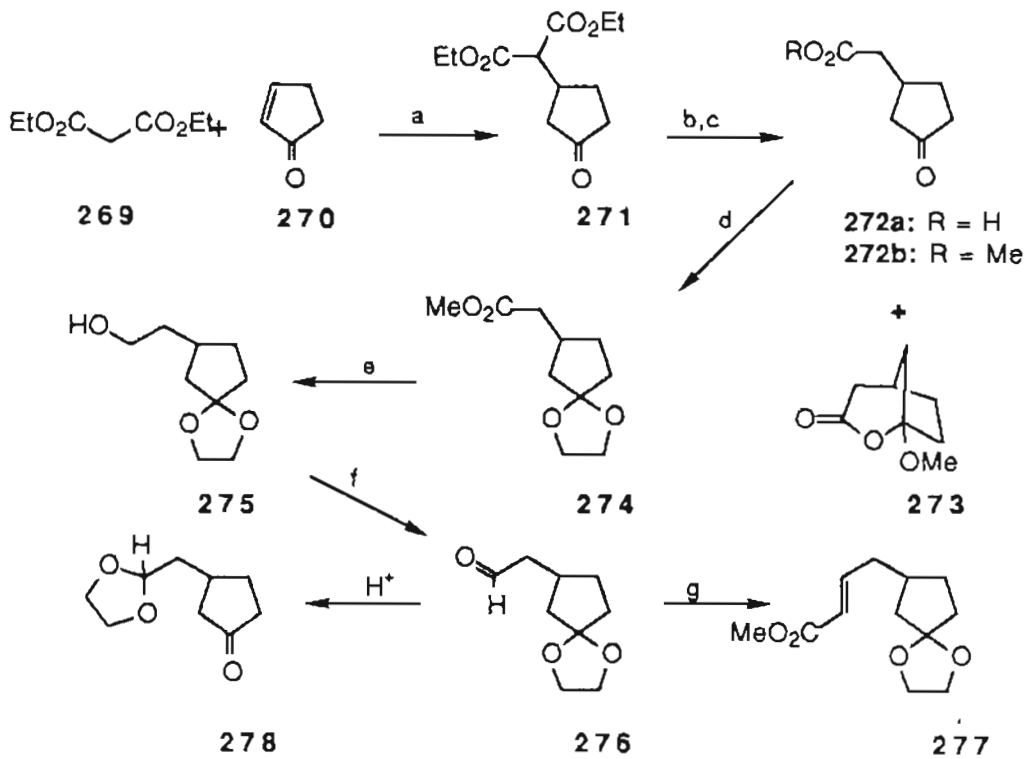
Introduction of the double bond at C-2,3 by selenation and elimination of the selenoxide[106] and then reduction of the ketone would give the alcohol **292b**. Conversion of **292b** to the mesylate **292a** and then elimination of the mesyl group through deprotonation to give a diene, would be followed by conversion of the carboethoxy group into an acetyl[107] group, furnishing **293**. Deprotection of the diol and oxidation of the benzylic hydroxyl[84] would give the ketone **294**. *Cis*-hydroxylation[82] of the isolated double bond on the convex face, followed by cleavage of the methyl ethers would give pillaromycinone (**140a**).

Scheme 2.25 Retrosynthetic Analysis



The Michael acceptor was prepared as shown in Scheme 2.26. Conjugate addition of diethyl sodiomalonate to 2-cyclopentenone (**270**) gave **271** in 90% yield,[108] which on acid hydrolysis and decarboxylation furnished the keto acid **272a**. Esterification of **272a** with methanol and sulfuric acid containing a small amount of water provided the ester **272b** in 65% yield. The addition of water was crucial since esterification under anhydrous conditions gave predominantly the undesired lactone **273**. Protection of the ketone by treatment of **272b** with ethylene glycol and

Scheme 2.26

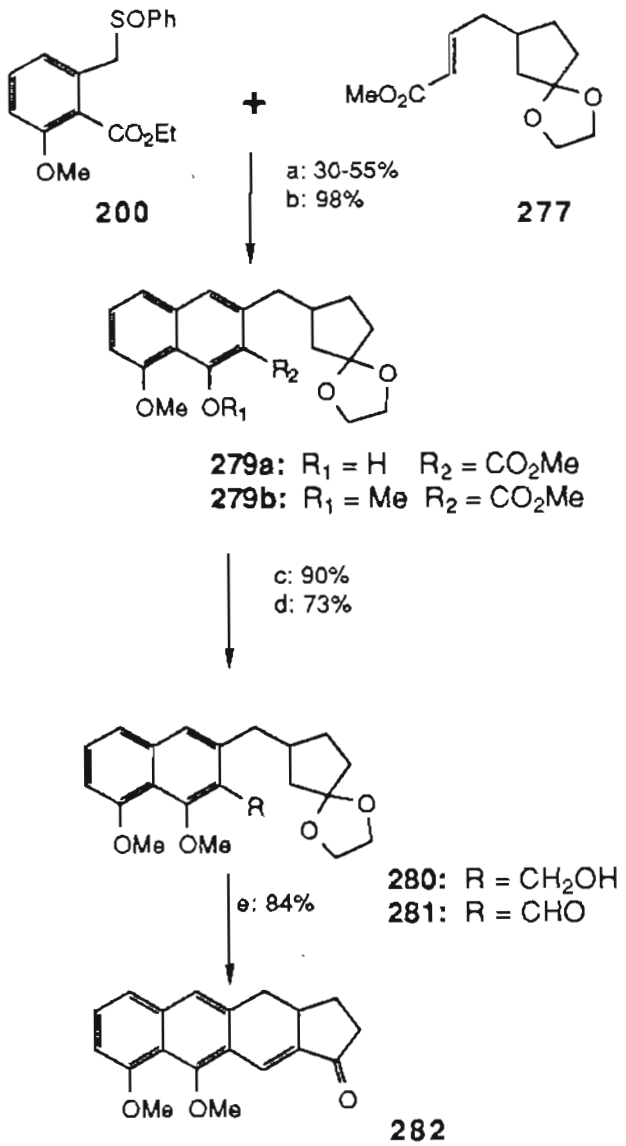


a. NaOEt, EtOH b. H_2SO_4, H_2O, AcOH c. H_2SO_4, MeOH, H_2O
d. $HOCH_2CH_2OH$, PyH^+TsO^-, Benzene e. LAH, Et_2O
f. $CrO_3 \cdot 2Py$, CH_2Cl_2 g. $(MeO)_2P(O)CH_2CO_2Me$, NaH, DMF

pyridinium toluenesulfonate[109] gave the ketal **274** (91%), which was immediately reduced with lithium aluminum hydride (88%)[110] to the alcohol **275**. Collins oxidation[62] of **275** gave the aldehyde **276** in 79% yield. The aldehyde proved to be very acid sensitive. Trace amounts of acid resulted in a transketallization process with formation of **278**. For this reason, the aldehyde **276** was reacted immediately with the anion of trimethylphosphonoacetate.[102] Chromatography furnished the Michael acceptor **277** as a mixture of E,Z isomers in 56% yield.

Condensation of the anion of the sulfoxide **200** with the Michael acceptor **277**,[54] as shown in Scheme 2.27, gave the naphthalene **279a**, but in variable and modest yield (30%). Modification of the anion of **200** through addition of copper(I) cyanide did not improve the reaction. Subsequent methylation of **279a** with dimethyl sulfate gave the dimethyl ether **279b** in 98% yield. Lithium aluminum hydride reduction of **279b** gave the alcohol **280** (90%), which on Collins oxidation[62] furnished the aldehyde **281** in 73% yield. Hydrolysis of the ketal in **281** with dilute perchloric acid[111] in tetrahydrofuran produced a transitory keto aldehyde intermediate, which underwent further intramolecular aldol cyclization, furnishing the tetracyclic enone **282** as orange crystals in 84% yield.

Scheme 2.27

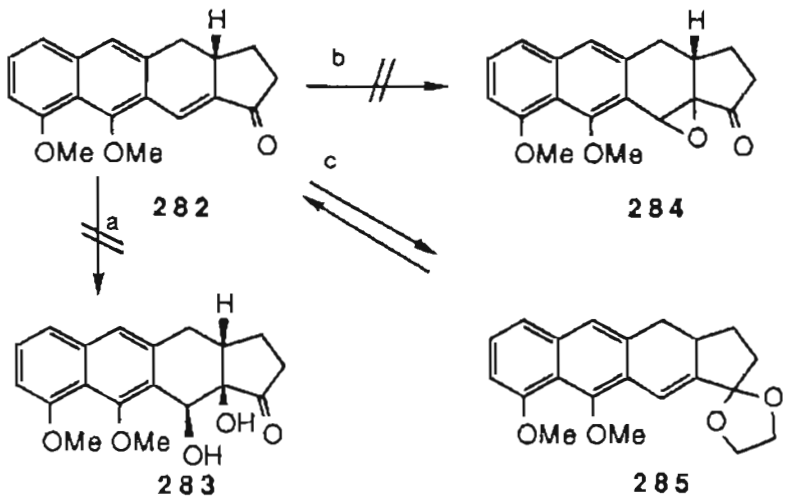


a. LDA, THF b. Me_2SO_4, K_2CO_3, MEK c. LAH, Et_2O
d. CrO_3:Py, CH_2Cl_2 e. $HClO_4$, H_2O, THF

As shown in Scheme 2.28 the unsaturated enone fragment in **282** proved to be unexpectedly resistant to either hydroxylation[82] or epoxidation.[112] Treatment of **282** with catalytic osmium tetraoxide and trimethylamine-N-oxide in aqueous acetone failed to give the expected diol **283**. Olefins conjugated to a carbonyl group are deactivated toward reaction with osmium tetraoxide due to decreased electron density. Although an olefin conjugated to either a carbonyl or an aromatic ring can be hydroxylated, conjugation to both an aromatic ring and a carbonyl apparently results in complete deactivation.

As an alternative to direct hydroxylation, epoxidation of **282** was attempted; however, none of the epoxide **284** was formed when **282** was reacted with *tert*-butylhydroperoxide and Triton-B. In order to remove

Scheme 2.28

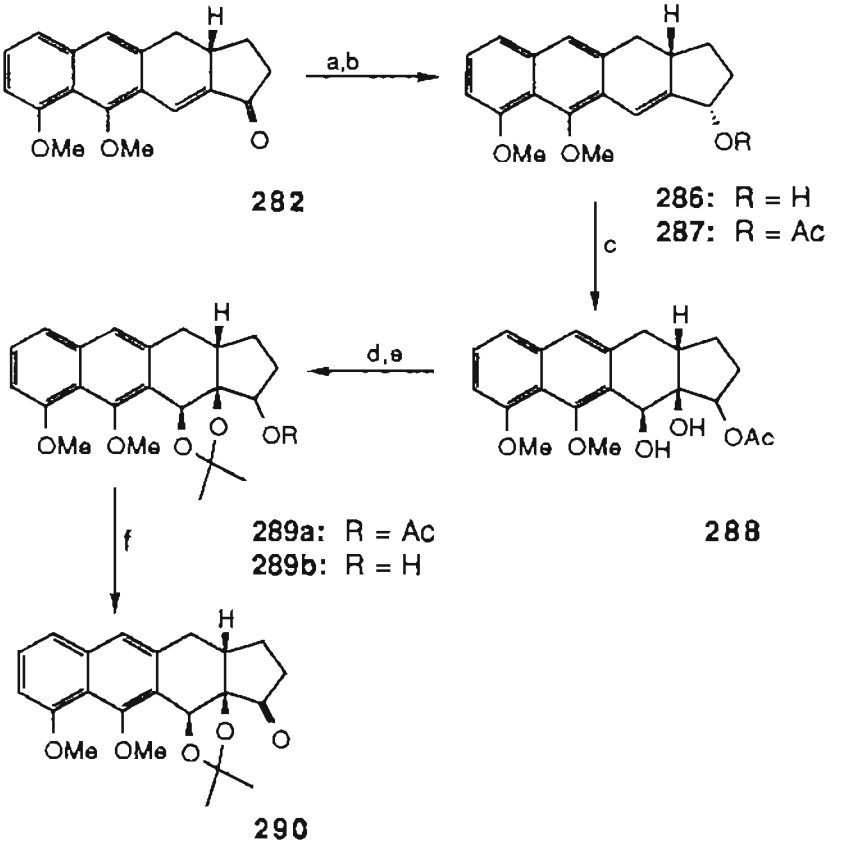


a. OsO_4, TMNO, H_2O, acetone b. t-BuOOH, Triton B, benzene
c. $HOCH_2CH_2OH$, PyH^+TsO^-, benzene

the deactivating influence of the carbonyl group on the double bond, preparation of the ketal **285** was attempted. Treatment of **282** with ethylene glycol and pyridinium toluenesulfonate[109] in benzene produced the ketal **285** as judged by thin layer chromatographic analysis. However, upon workup and isolation, the product was found to be a 1:1 mixture of starting material and ketal. Apparently, the ketal **285** was unstable and readily underwent hydrolysis back to the ketone.

Removal of the deactivating effect of the ketone through reduction of the ketone to an alcohol was examined as shown in Scheme 2.29. In order to obtain the endo alcohol **286** so that subsequent hydroxylation on the exo face would not be sterically hindered in any way, a bulky reducing agent was employed. Treatment of **282** with sodium dimethoxyethoxyaluminum hydride (Red-Al)[113] gave the alcohol **286** (77%) which was converted to the acetate **287** in near quantitative yield. The presence of acetate peaks at 2.04 and 2.09 ppm (δ) in the ^{1}H-NMR spectrum indicated that **287** was an 8:2 mixture of endo and exo alcohols. Hydroxylation of **287** with osmium tetraoxide and trimethylamine N-oxide[82] gave the diol **288** in 58% yield as a mixture of isomers. Mass spectrometry gave the expected molecular weight of *m/z* 372 (M^+). Treatment of **288** with 2,2-dimethoxypropane[114] gave the acetonide **289a** in 37% yield. Hydrolysis of the acetate group in **289a** with potassium carbonate in methanol gave the alcohol **289b** in 87% yield, and subsequent Collins[62] oxidation furnished the ketone **290** in 92% yield. Based on steric considerations, **290** most likely has the *cis* fused A and B rings.

Scheme 2.29



a. Red-Al, DME, b. Ac_2O, Py, Et_2O c. OsO_4, TMNO, H_2O, acetone
d. 2,2-dimethoxypropane, PyH^+OTs^- e. K_2CO_3, MeOH, f. $CrO_3 \cdot 2Py$, CH_2Cl_2

In this approach to the synthesis of pillaromycinone, aldol cyclization proved to be a successful method for fabrication of the tetracyclic intermediate **282**; however, the conjugated double bond proved to be inert to hydroxylation or epoxidation. This problem was overcome through reduction of the ketone to an alcohol and thus by an indirect route, the protected diol **290** was obtained.

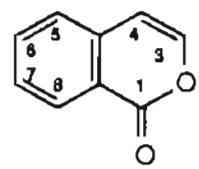
There were several steps that were accomplished with only modest results. Acetonide formation proved to be a poor reaction and it was suspected that this was due to the acid lability of the benzylic hydroxyl group. Although Red-Al reduction proceeded in good yield, the reduction was not stereospecific and resulted in a mixture of isomers. Use of other more bulky reducing agents would have to be examined to alleviate the problem. The inability to directly hydroxylate the double bond in **282** necessitated that several steps be added to the sequence in order to overcome the deactivating influence of the ketone.

A particularly troublesome aspect of the sequence was the modest yield of the naphthalene **279a** prepared from the condensation of the sulfoxide **200** with the acceptor **277**. Although a variety of conditions were examined, the reaction could not be improved. These results led us to explore alternate methods for fabrication of naphthalene intermediates.

Part III: ISOCOUMARINS

I. Introduction

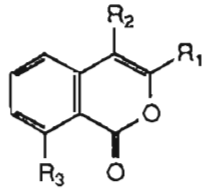
A class of compounds containing the 1(H)-2-benzopyran-1-one ring system (Figure 3.1) are commonly known as isocoumarins. They occur widely in nature and possess a range of interesting biological activities.[115] The isocoumarins shown in Figures 3.2 and 3.3 are representative of the structural diversity found among these compounds.



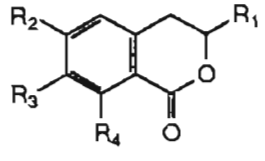
300: Isocoumarin

Figure 3.1

While a variety of methods have been developed for the preparation of this seemingly simple ring system, there are no efficient and general methods for their synthesis.

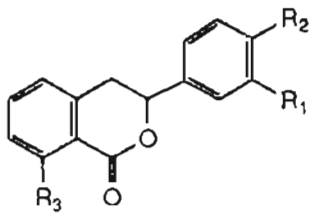


		R_1	R_2	R_3
301 a:	3-Methyl-8-hydroxyisocoumarin	Me	H	OH
301 b:	3-Propylisocoumarin	Pr	H	H
301 c:	Artemidin	-CH=CHCH$_2$CH$_3$ (E)	H	H
301 d:	3,4-Dimethyl-8-hydroxyisocoumarin	Me	Me	OH
301 e:	3-(1,2-Dihydroxyethyl)isocoumarin	-CH(OH)CH$_2$OH	H	H

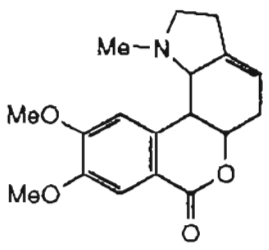


		R_1	R_2	R_3	R_4
301 f:	Mellein	Me	H	H	OH
301 g:	Kigelin	Me	OMe	OMe	OH
301 h:	Glomellin	Pr	OMe	H	OH
301 i:	Capillarin	-CH$_2$CCCH$_3$	H	H	H
301 j:	6,8-Dimethoxyisocoumarin-3-carboxylic acid	-CO$_2$H	OMe	H	OMe

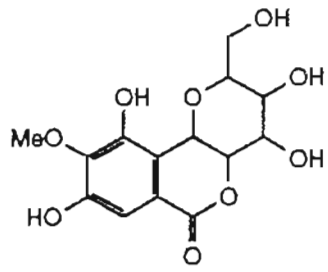
Figure 3.2



		R_1	R_2	R_3
302 a:	Phylodulcinol	OH	OMe	OH
302 b:	Hydrangenol	H	OH	OH
302 c:	Dihydrohomalicine	O-D-glucose	H	H



302 d: Homolycorine

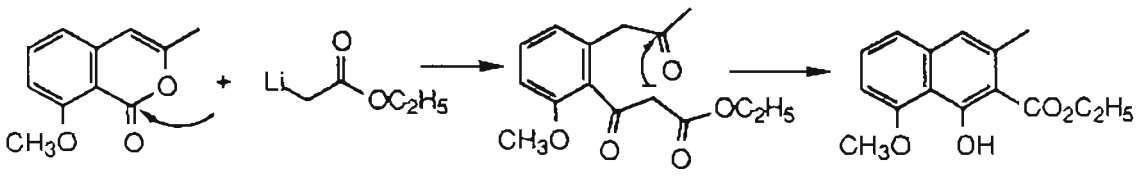


302 e: Bergenin

Figure 3.3

The unsatisfactory yield that was encountered in our efforts to prepare substituted hydroxynaphthalenes through Michael reaction of sulfoxides with unsaturated esters led us to pursue a radically different approach. A conceivably efficient and general approach to hydroxy-naphthalenes is based on their derivation from isocoumarins. Hauser and Pogany had reported, as shown in Scheme 3.1, that treatment of the isocoumarin **303** with lithio ethyl acetate furnished the 1-hydroxy-naphthalene **306** in high yield.[116]

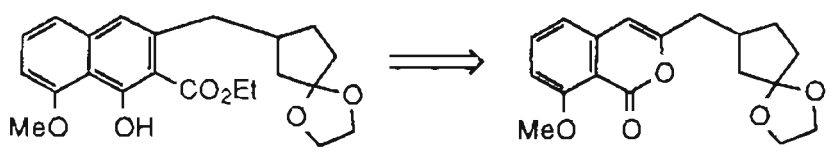
Scheme 3.1



303 **304** **305** **306**

Application of this methodology for the preparation of naphthalene **307** would then require an efficient synthesis of the isocoumarin **308** (Scheme 3.2). However, the inadequacy of the existing methods for the preparations of highly functionalized isocoumarins, led us to explore new approaches for the construction of these compounds.

Scheme 3.2



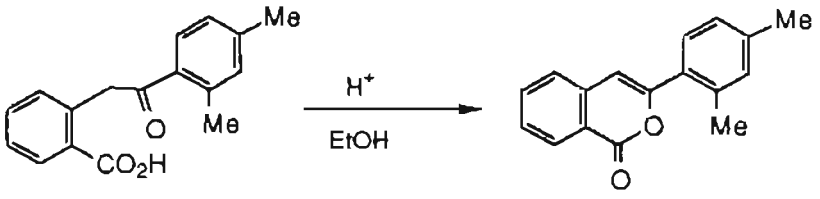
307 **308**

II. Synthetic Background

A. Cyclization

A number of methods have been developed for synthesis of isocoumarins. The simplest and most direct method involves cyclization and dehydration of *ortho*-substituted benzoic acids as shown in Scheme 3.3. In this manner, 2-carboxybenzyl 2,4-dimethylphenyl ketone (**309**) has been cyclized to the isocoumarin **310** with sulfuric acid in ethanol.[117]

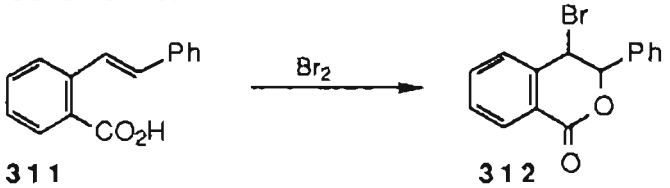
Scheme 3.3



309 **310**

A related preparation involves the cyclization of *ortho*-vinyl benzoic acids as shown in Scheme 3.4. For example, treatment of stilbene-2-carboxylic acid (**311**) with bromine yields the halogenated dihydroisocoumarin **312**.[118]

Scheme 3.4



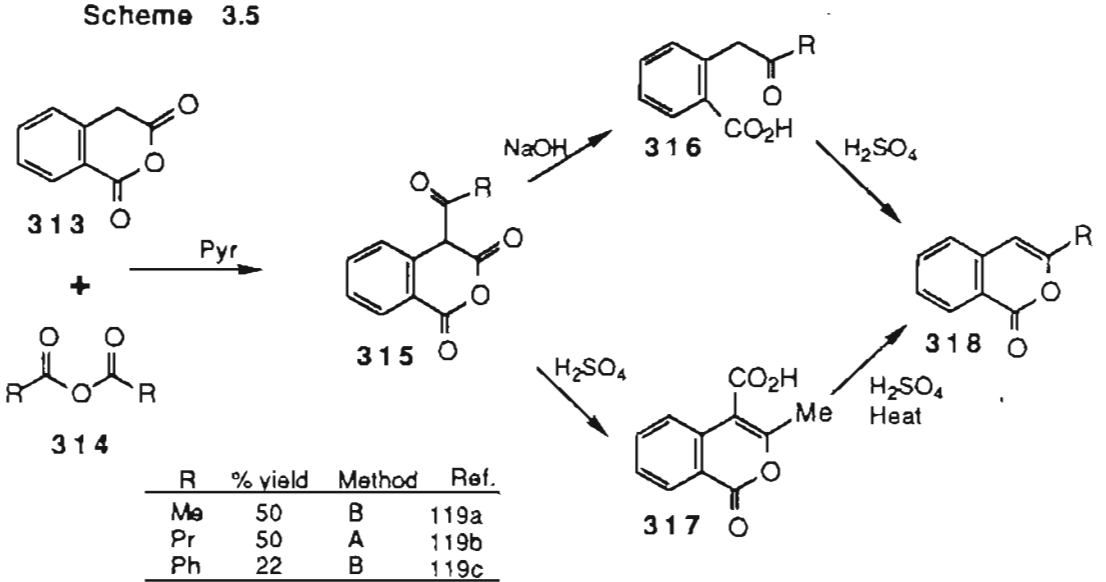
311 **312**

In contrast to the above mentioned preparations, the synthesis of isocoumarins from smaller fragments is of greater preparative utility. A variety of condensation methods have been developed to prepare isocoumarins with various substitution patterns.

B. Acylation With Acid Anhydrides

Simple isocoumarins can be made directly from homophthalic anhydride (**313**) through acylation with carboxylic acid anhydrides **314** as shown in Scheme 3.5.[119] The initially acylated products **315** are hydrolyzed to the keto acids **316**, which are then cyclized to the 3-substituted isocoumarins **318** by acid catalysis. Alternatively, treatment of the initially acylated product **315** with sulfuric acid leads to the rearranged intermediate **317**. Upon prolonged heating in sulfuric acid,

Scheme 3.5

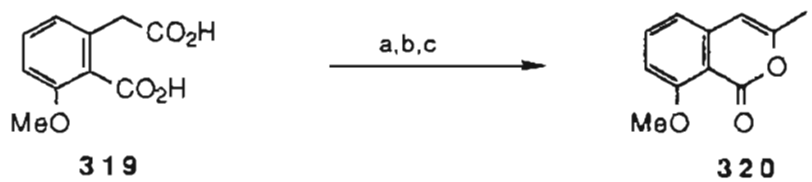


R	% yield	Method	Ref.
Me	50	B	119a
Pr	50	A	119b
Ph	22	B	119c

decarboxylation occurs furnishing the isocoumarins **318**. In this manner, methyl, propyl, and phenyl substituted isocoumarins have been prepared in 20-50% yields.

Similarly, Hauser and Rhee reported the preparation of 3-methyl-8-methoxyisocoumarin (**320**) in 68% yield from the methoxy homophthalic acid **319** as shown in Scheme 3.6.[120] Acylation of **319** with acetic anhydride and pyridine, then hydrolysis and decarboxylation, followed by cyclization and dehydration with perchloric acid produced **320**.

Scheme 3.6 Hauser and Rhee



319 **320**

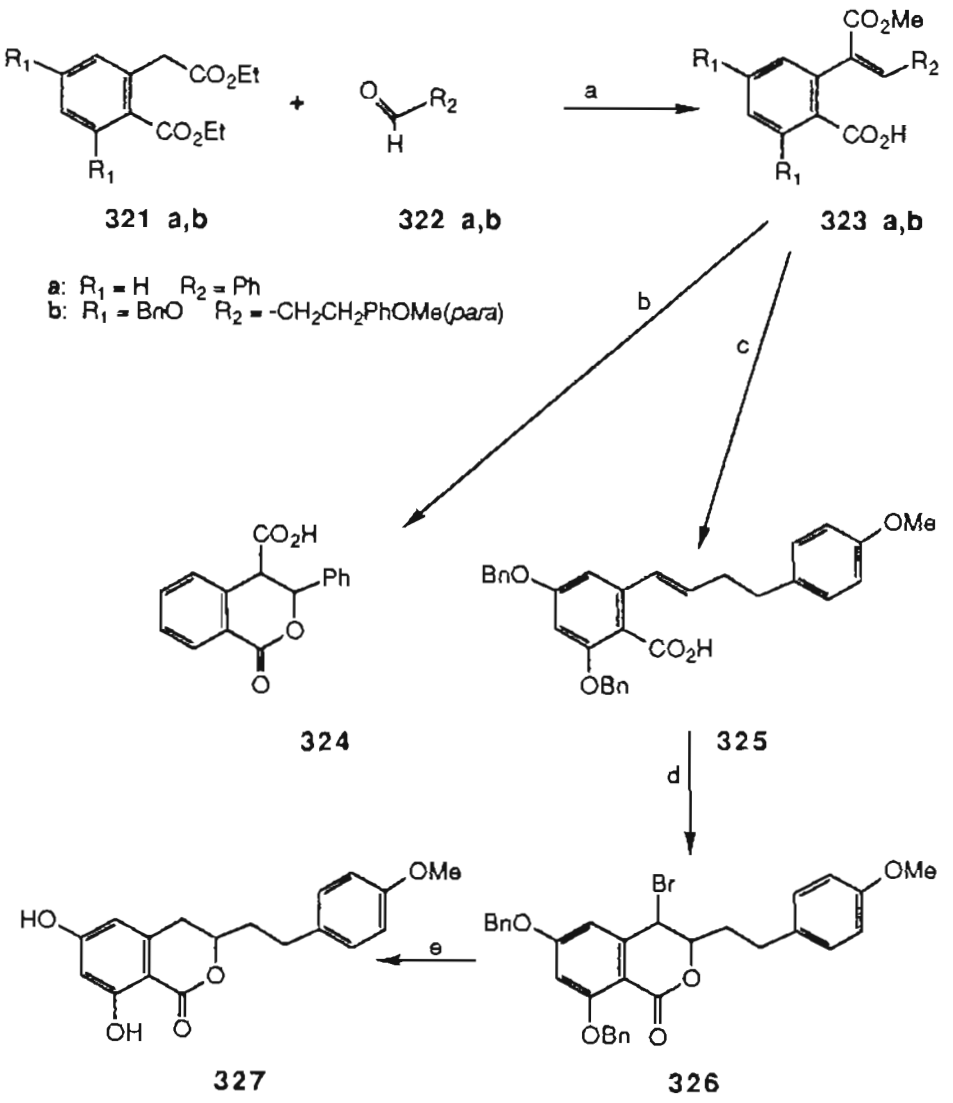
a. Ac_2O, py b. OH^- c. $HClO_4$, Ac_2O

While acid anhydride acylation of homophthalic anhydrides can be reasonably efficient, it is limited to reactions simple anhydrides. Its other disadvantages are that the anhydride must be used in a large excess and that half of the acyl component is unused.

C. Stobbe Condensation

Stobbe condensation of aldehydes and ketones with homophthalate esters has also been used to prepare isocoumarins as shown in Scheme 3.7. Condensation of the homophthalate ester **321a** with benzaldehyde (**322a**)

Scheme 3.7 Stobbe condensation

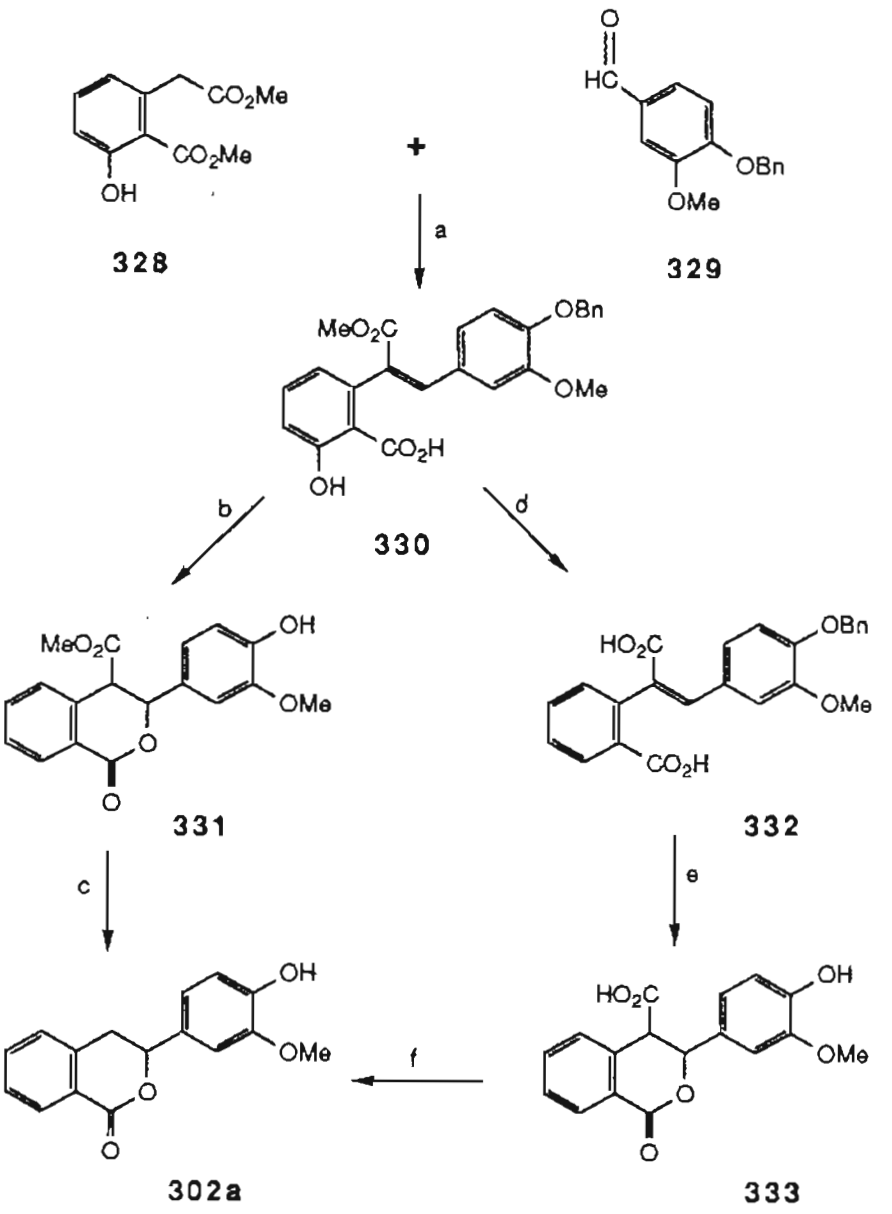


a. NaH, benzene b. H_2SO_4 c. NaOH, DMF, reflux
d. Br_2, $CHCl_3$ e. H_2, Pd-C, Et_3N

in the presence of sodium hydride yields the half ester **323a**.[121] On treatment with acid, **323a** is converted into 3-phenyl-3,4-dihydro-isocoumarin-4-carboxylic acid (**324**). In a variation of this method, diethyl 3,5-dibenzyloxyhomophthalate (**321b**) was condensed with 3-(4-methoxyphenyl)propionaldehyde to give the half ester **323b**[122] in 31% yield. Hydrolysis and decarboxylation of **323b** with sodium hydroxide in refluxing dimethylformamide furnished **325** in 54% yield. Cyclization of **325** with bromine gave the 4-bromodihydroisocoumarin **326** (44%). Catalytic debromination and debenzylation provided agrimonolide (**327**) in 40% yield. The overall yield of **327** from **321b** and **323b** was only 3%.

Phylodulcin has been prepared similarly as shown in Scheme 3.8.[123] Stobbe condensation of the homophthalate ester **328** with the substituted benzaldehyde **329** furnished the half ester **330** in 80-90% yield. Cyclization of **330** to **331** was achieved with hydrogen bromide in 80% yield. Treatment of **331** with aluminum bromide in an aqueous solution at 110-125 °C gave phylodulcin **302a** in 17% yield. Better yields of **302a** were obtained through a longer sequence. Base hydrolysis of **330** produced the diacid **332** in 80-90% yield. Cyclization and debenzylation of **332** to **333** was achieved in one step by treatment with hydrogen bromide in acetic acid in 80% yield. Heating an aqueous solution of **333** at 140 °C in an autoclave produced DL-phylodulcin (**302a**) in 47% yield or 27% from **328** and **329**. While the Stobbe condensation gives good yields with aromatic aldehydes, drastic conditions are required and, as was observed above, the yields with aliphatic aldehydes can be quite poor.

Scheme 3.8 Phylodulcin

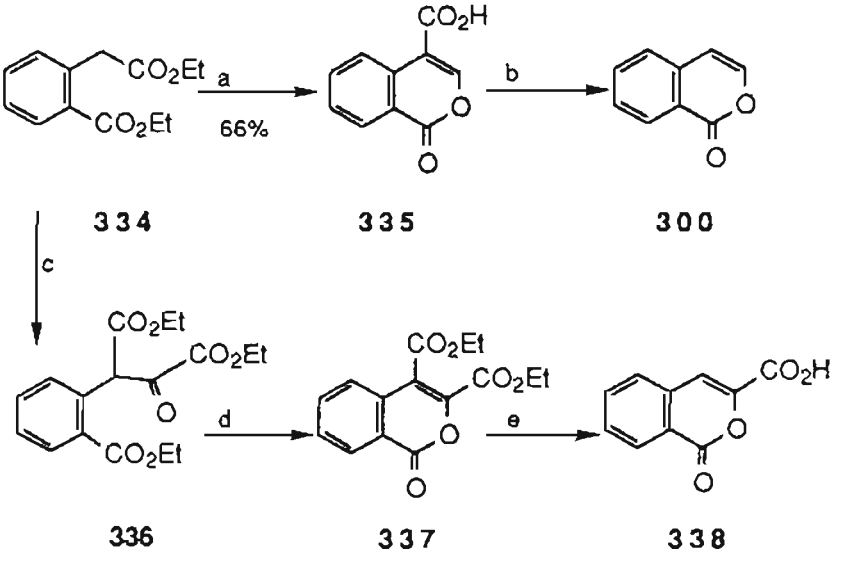


a. NaH b. HBr c. $AlBr_3$, 110-125° C
d. OH^- e. HBr f. 140°C

D. Claisen Condensation

Claisen condensation of homophthalate esters with alkyl esters has been used to prepare isocoumarins, as shown in Scheme 3.9. Condensation of homophthalate ester **334** with methyl formate furnished isocoumarin-4-carboxylic acid (**335**).[124] Decarboxylation of **335** with phosphoric acid yielded the parent isocoumarin **300**. Alternatively, Claisen condensation of **334** with diethyl oxalate gives the triester **336** which upon heating undergoes elimination of ethanol to furnish the isocoumarin diester **337**.[125] Prolonged hydrolysis at 180 °C yields isocoumarin-3-carboxylic acid (**338**). While these are reasonable procedures, the scope of this approach is limited to carboxy substituted isocoumarins.

Scheme 3.9 Claisen condensation

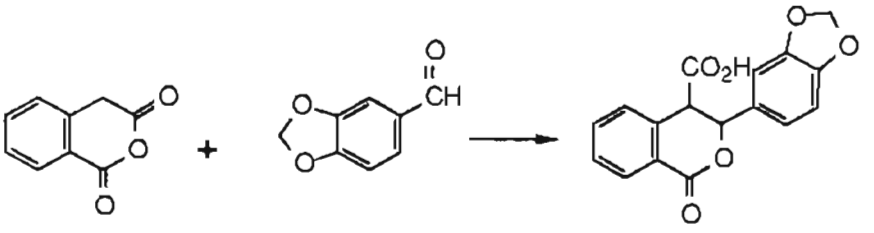


a. $NaOEt$, HCO_2CH_3 b. H_3PO_4
c. Na, EtO_2CCO_2Et d. Heat e. H_2O, 180°

E. Perkin Condensation

The Perkin condensation of homophthalic anhydrides with aromatic aldehydes has also been used to prepare isocoumarins (Scheme 3.10).[126] The enolate anion of **313**, prepared with the triphenylmethyl anion in benzene was isolated and suspended in ether. Reaction of the enolate with piperonal (**339**) for seven days at room temperature furnished the isocoumarin **340** in 20% yield. Alternatively, condensation of **313** and **339** with sodaamide in liquid ammonia furnished **340** in 66%

Scheme 3.10 Perkin Condensaton



313 **339** **340**

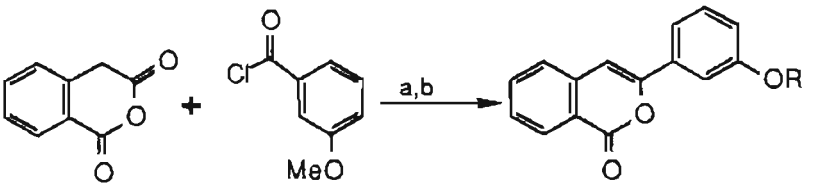
Method A: triphenylmethyl sodium, benzene, ether
Method B: Na, NH_3 (liq), benzene

F. Acylation With Acid Chloride

The aglycone of homalicine (**342b**) has been prepared by acylation of homophthalic anhydride as shown in Scheme 3.11.[127] Simultaneous addition of *meta*-methoxybenzoyl chloride (**341**) and aluminum chloride

to a suspension of homophthalic anhydride (**313**) in nitrobenzene gave the isocoumarin **342a** in 16% yield. Demethylation with hydriodic acid in acetic acid at 140 °C furnished the aglycone of homalicine **342b** in 82% yield.

Scheme 3.11 Homalicine



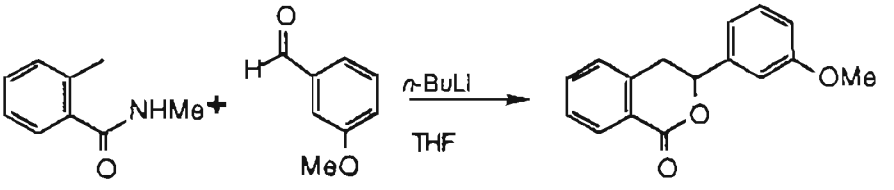
313 **341** **342 a:** R = Me
342 b: R = H

a. $AlCl_3$, nitrobenzene b. HI, AcOH, 140°C

G. Condensations With Lithiated Carbanions

Recently, a variety of approaches to isocoumarins from metallated organic intermediates have been described. Scheme 3.12 shows the preparation of the methyl ether aglycone of dihydrohomalicine (345)[127] through condensation of the dilithio anion of N-methyl-*ortho*-toluamide (343) with 3-methoxybenzaldehyde in 13% yield.

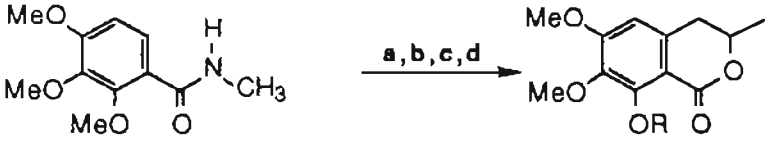
Scheme 3.12 Dihydrohomalicine



343 **344** **345**

Kigelin has been prepared as shown in Scheme 3.13.[128] *Ortho*-metalation of the trimethoxybenzamide **346** was accomplished with a 5 molar excess of *n*-butyllithium under reflux for 1 hour. Alkylation of the anion with propylene oxide, followed by alkaline hydrolysis, gave the isocoumarin **347** in 35% yield. Demethylation with aluminum chloride furnished racemic kigelin (**301f**) in 70% yield.

Scheme 3.13 Kigelin



346

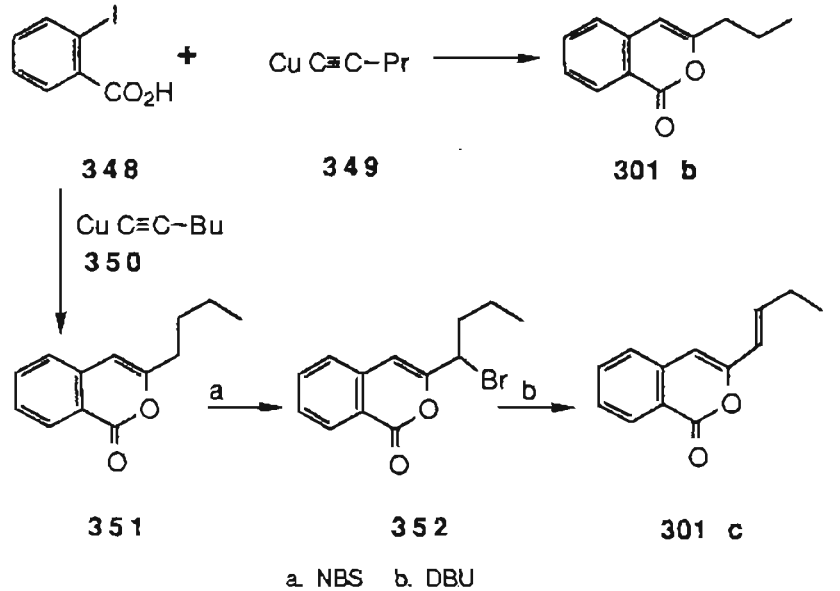
347 : R = Me
301 f: R = H

a. *n*-BuLi b. Propylene Oxide c. OH^- d. $AlCl_3$

H. Condensation With Organocuprates

Artemidin and 3-propyl isocoumarin have been prepared by coupling *ortho*-iodobenzoic acid with copper acetylide as shown in Scheme 3.14.[129] Treatment of **348** with cuprous *n*-propylacetylide (**349**) in dimethylformamide under reflux for 4 days gave 3-*n*-propyl-isocoumarin (**301b**) in 60% yield. Coupling of **348** with cuprous *n*-butylacetylide (**350**) furnished 3-butylisocoumarin **351** in 78% yield. Allylic bromination of **351** (47%) gave the bromoisocoumarin **352**, which upon dehydrohalogenation with DBU gave artemidin (**301c**).

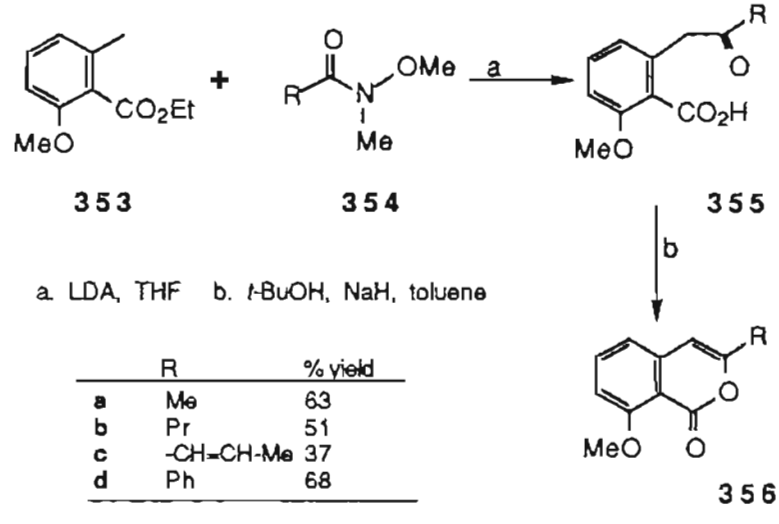
Scheme 3.14 3-Propylisocoumarin



I. Acylation With Amides

Recently, Staunton and coworkers have described a convenient method for fabrication of isocoumarins and this is shown in Scheme 3.15.[130] Condensation of the anion of 2-methyl-6-methoxybenzoate (**353**) with N-methoxy-N-methyl amides **354** gave the ketones **355**. Treatment of the ketones **355** with sodium hydride and a catalytic amount of *t*-butanol furnished the isocoumarins **356** in 40-70% overall yield.

Scheme 3.15 Staunton



353 **354** **355** **356**

a. LDA, THF b. *t*-BuOH, NaH, toluene

	R	% yield
a	Me	63
b	Pr	51
c	-CH=CH-Me	37
d	Ph	68

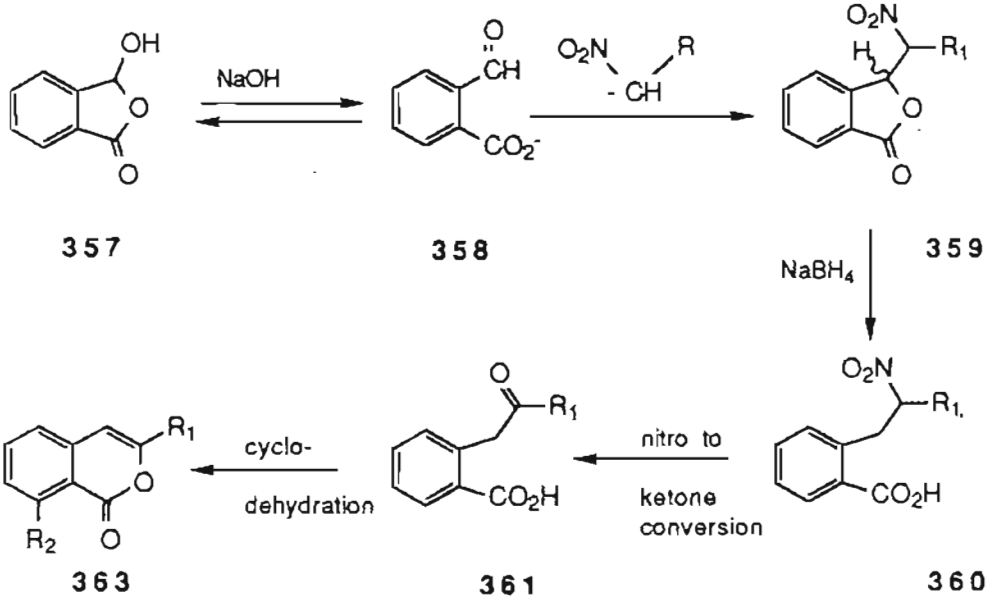
In conclusion, the foregoing procedures are limited primarily to the preparation of 3-phenyl substituted isocoumarins. Only a few are appropriate for synthesis of 3-alkyl substituted isocoumarins, and for the most part, they require strongly basic conditions, precursors which are difficult to prepare, and often proceed in low overall yield.

III. Synthesis of Isocoumarins

A. Nitro Aldol Condensation

The absence of satisfactory methods to the needed isocoumarin **308** led us to devise a fundamentally new approach to isocoumarins and this is shown in outline form in Scheme 3.16. It has been reported that condensation of nitromethane with phthalaldehydic acid **357** furnished the 3-nitromethylphthalide **359**.[131] The reaction proceeds through an aldol condensation of the anion of nitromethane with the intermediary carboxyaldehyde **358**, which exist in equilibrium with **357** in the presence of base. The initially formed hydroxy nitro acid cyclizes to the

Scheme 3.16 Proposed Isocoumarin Synthesis



lactone **359** upon acid workup. It was anticipated that reductive cleavage of the lactone in **359** would furnish the nitro acid **360**. In subsequent steps the nitro group would be converted to a carbonyl funtionality to give **361**, which could be cyclized and dehydrated to the isocoumarin **363**.

Although there were several literature reports describing the condensation of phthalaldehydic acid with nitroalkanes,[132] these were limited primarily to condensations with nitromethane and nitroethane. While procedures have been described for the reductive elimination of β-acetoxy nitro compounds to nitroalkanes,[133] application of this reaction to nitromethylphthalide had not been reported. Likewise, conversion of 2-(2-nitroalkyl)benzoic acids to keto acids has not been described.

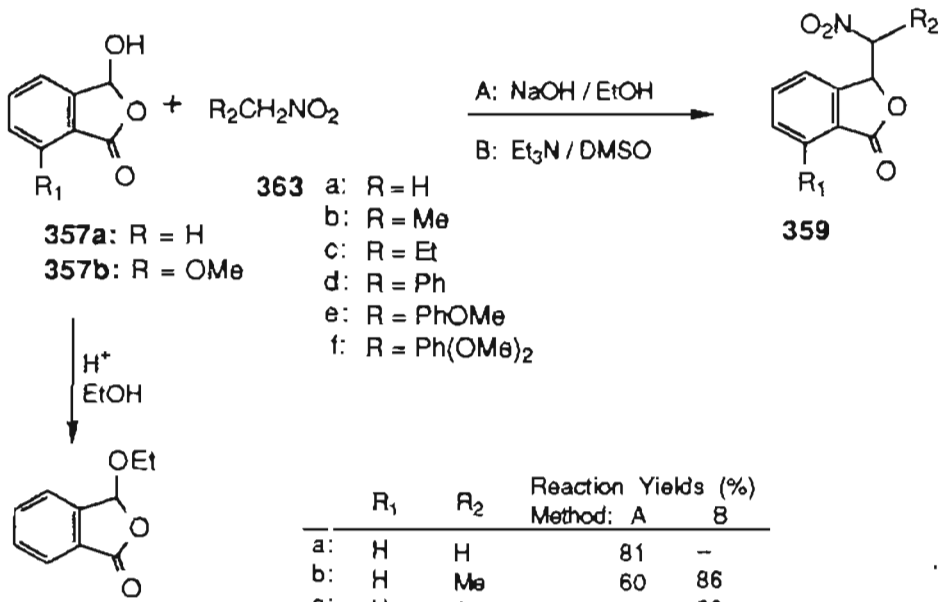
If successful, this approach to the synthesis of isocoumarins would overcome some of the problems noted previously. An equimolar stoichiometry of phthalaldehydic acid and nitro compound was anticipated. Furthermore, the reaction conditions for the overall synthesis were anticipated to be reasonably mild with no special precautions required.

The Henry condensation reaction of *ortho*-phthalaldehydic acid with a number of nitro compounds was examined and the results are shown in Scheme 3.17. Repetition of the condensation of phthalaldehydic acid (**357a**) with nitromethane employing sodium hydroxide in ethanol gave the lactone (**359a**) in 81% yield. Condensation with nitroethane also worked reasonably well furnishing **359b** after 2 days in 60% yield. A major by-product was 3-ethoxyphthalide (**364**) produced by solvent interaction with **357a**, and was verified by treatment of **357a** with hydrochloric acid in ethanol to give **364**. Condensation with nitropropane

also worked, however the yield was only 38%. To further explore the scope of the reaction, the condensation of **357a** with phenylnitromethane was also examined, but there was no reaction.

A number of different base and solvent systems were examined and triethylamine in dimethyl sulfoxide was found to be the best. Condensation of phthalaldehydic acid with nitroethane, nitropropane, and phenylnitromethane gave the lactones **359b,c,d** in 86, 69, and 65% yields respectively. Triethylamine appeared to be too weak a base to deprotonate nitromethane and in that case, sodium hydroxide in ethanol provided the best yield.

Scheme 3.17



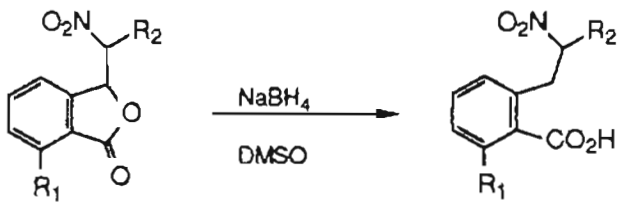
	R_1	R_2	Reaction Yields (%) Method: A	B
a:	H	H	81	–
b:	H	Me	60	86
c:	H	Et	39	69
d:	H	Ph	0	65
e:	OMe	Me		79
f:	OMe	PhOMe		45
g:	OMe	$Ph(OMe)_2$		40

The condensation was also explored with 7-methoxyphthal-aldehydic acid **357b**. Condensation of **357b** with nitroethane, 4-methoxy-phenylnitromethane, and 3,4-dimethoxyphenylnitromethane gave the phthalides **359e,f,g** in 40-79% yield. Although condensation of **357a** with phenylnitromethane gave good results, condensation of **357b** with the methoxy substituted phenylnitromethanes gave modest results.

B. Lactone Cleavage

With the β-nitrolactones on hand, reductive cleavage of the lactone functionality was examined (Scheme 3.18). Reduction of the nitrolactones **359** with sodium borohydride in dimethyl sulfoxide consistently furnished the nitro acids **360** in 70-95% yield.[133]

Scheme 3.18



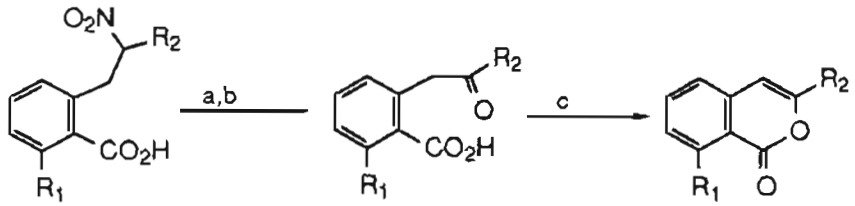
359 **360**

	R_1	R_2	% yield
a	H	H	93
b	H	Me	77
c	H	Et	70
d	H	Ph	85
e	OMe	Me	95
f	OMe	PhOMe	73
g	OMe	$Ph(OMe)_2$	80

C. Reductive Hydrolysis of the Nitro Group

Conversion of the nitro functionality into a carbonyl initially proved to be troublesome. The McMurry procedure using titanium trichloride,[134] which was reported to give good results, gave low yields as shown in Scheme 3.19. The dianions of the nitro acids were generated by treatment of **360** with sodium methoxide in THF. These were added to solutions of titanium trichloride and ammonium acetate in water to furnish upon workup the crude ketone products **361**. The crude products were generally not purified, but rather treated with perchloric acid and acetic anhydride[135] to effect cyclization to the isocoumarins **363**. The

Scheme 3.19



360 **361** **363**

a. NaOMe, MeOH b. $TiCl_3$ (20% in 6N HCl), NH_4OAc, H_2O
c. $HClO_4$, Ac_2O, EtOAc

	R_1	R_2	% yield
a	H	H	20
b	H	Me	52
c	H	Et	43
d	H	Ph	32
e	OMe	Me	27
f	OMe	PhOMe	20

yields tended to be modest and erratic. Working with titanium trichloride was difficult due to its sensitivity to oxygen and the requirement that large amounts of ammonium acetate be used as a buffer. This made isolation of the product difficult due to the formation of emulsions.

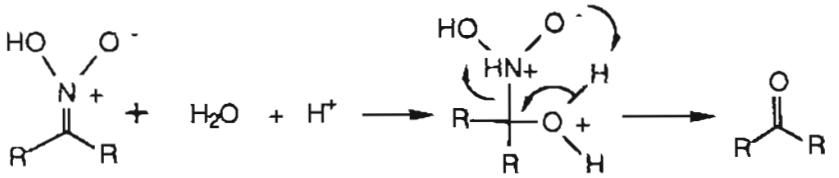
Other methods for the conversion of nitro groups into carbonyls were explored. Oxidative hydrolysis of nitroalkanes to carbonyl compounds with hydrogen peroxide and potassium carbonate[136] reportedly gives good results. Application of this procedure to the nitroacid **360b** did after cyclization yield some isocoumarin, but again the yields were erratic and low. We observed that the course of the reaction was independent of the hydrogen peroxide concentration and furthermore, the reaction proceeded in the absence of hydrogen peroxide. This led us to suspect that a simple Nef reaction was in operation, despite the presence of titanium trichloride or hydrogen peroxide.

D. Nef Reaction and Cyclodehydration

The Nef reaction is the conversion of a primary or secondary nitroalkane to an aldehyde or ketone.[137] In 1894, independent of the earlier work by Konovalov,[138] Nef[139] discovered the reaction and made a careful study of the conditions and products. The Nef reaction has achieved considerable importance in synthetic organic chemistry in recent years because of the commercial availability of many nitroalkanes. A particularly useful application of the Nef reaction has been in the field of

carbohydrate chemistry where it has been widely used to homologate sugars by one carbon.

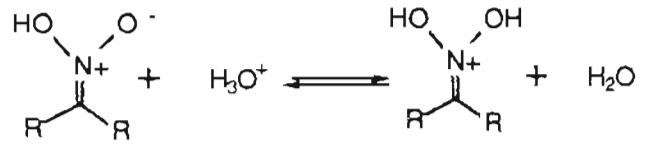
Although the mechanism of the reaction has not yet been rigorously established, a number of kinetic studies have been performed and a possible mechanism has been hypothesized. In 1951, van Tamelen and Thiede[140] proposed a mechanism consistent with the observation that the rate of hydrolysis is decreased by the steric hindrance of neighboring groups and by resonance stabilization. They concluded that addition of water to the carbon-nitrogen double bond in **364** to form **365** and its slow decomposition to **366** were the key steps (equation 3.1).



364 **365** **366**

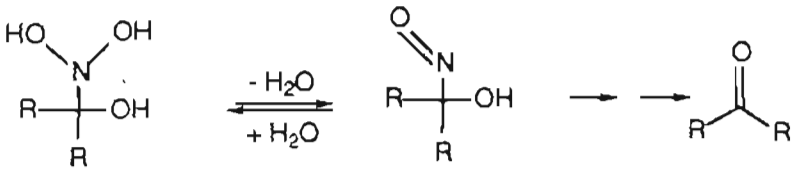
Equation 3.1

Shortly after, Hawthorne[141] performed kinetic studies of the Nef reaction and concluded that the rate determining transition state was composed of an *aci*-nitroalkane, a proton, and probably a molecule of hydroxylic solvent. Furthermore, the reaction was dependent on structure, a blue intermediate was formed, and resonance stabilization decreased the rate. It was postulated that an equilibrium involving the protonation of an *aci*-nitroalkane played an important role (equation 3.2). The blue color was attributed to a nitroso functionality and therefore it was presumed that **370** was an intermediate which could decompose to a carbonyl compound (equation 3.3).



367 368

Equation 3.2



369 370 366

Equation 3.3

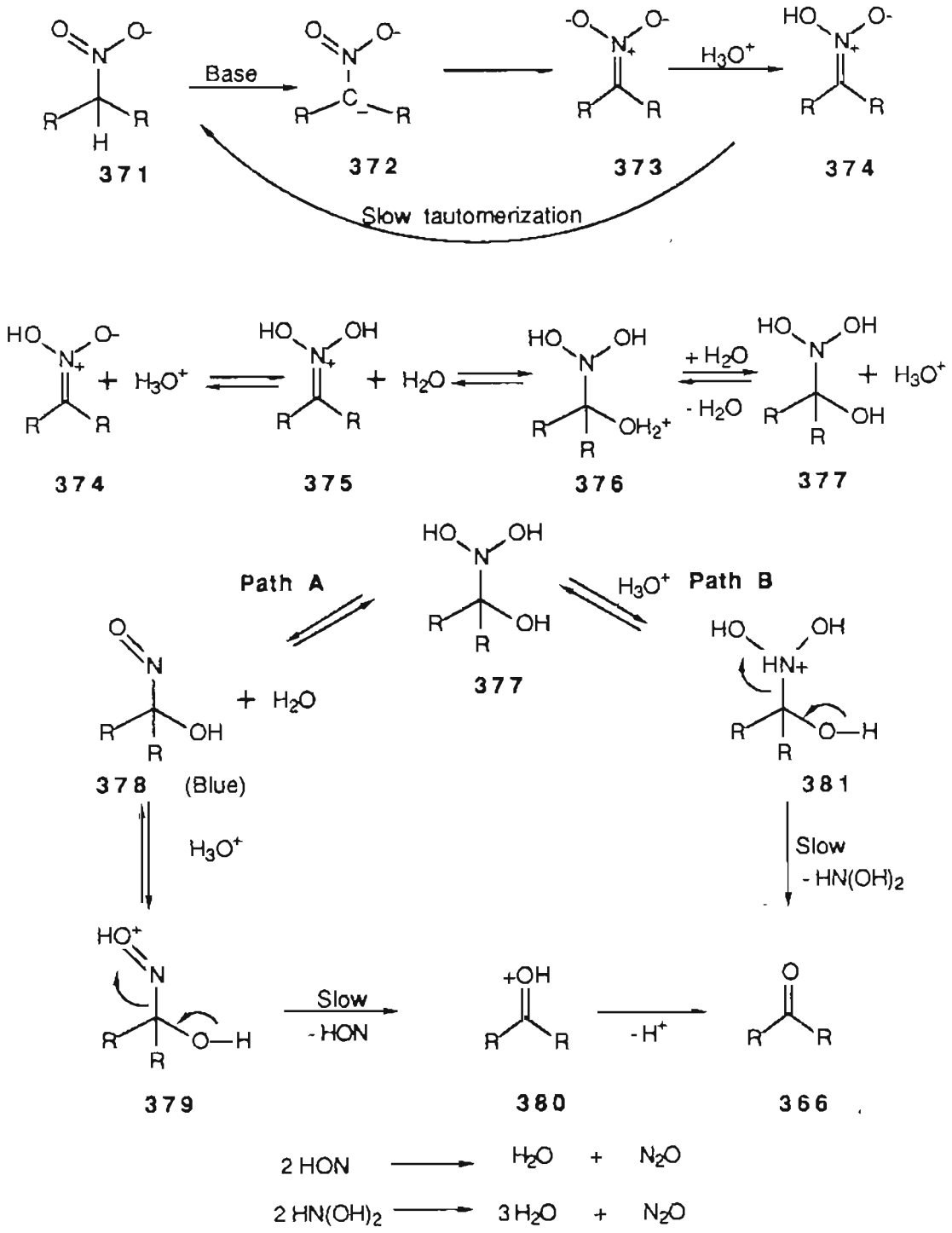
More recently, another kinetic study was performed by Sun and Folliard[142] (1971) who examined the participation of water in the Nef reaction. They obtained an experimental rate constant k_2 which could be expressed by the following equation,

$$k_2 = \frac{k_a}{[H_2O]} + k_b[H_2O]$$

where in one part there was a direct relationship to water and in another part there was an inverse relationship. These findings showed that there were two pathways to the reaction and these were similar to each of the mechanisms proposed earlier. Path B corresponded to van Tamelen and Thiede's mechanism and path A corresponded to Hawthorne's mechanism. The relative amount of reaction by each of these pathways was found to be dependent on the water concentration.

Sun and Folliard's mechanism is shown in Scheme 3.20. Treatment of the nitroalkane **371** with a strong base resuits in deprotonation to give the anion **372** which rearranges to the *aci*-anion **373**. Protonation of **373** gives the *aci*-nitroalkane **374** which only very slowly rearranges back to

Scheme 3.20


Base
H_3O^+
371
372
373
374
Slow tautomerization
$+ H_2O$
$- H_2O$
375
376
377
Path A
Path B
378 (Blue)
381
Slow
$- HN(OH)_2$
379
Slow
$- HON$
380
$- H^+$
366
$2\,HON \longrightarrow H_2O + N_2O$
$2\,HN(OH)_2 \longrightarrow 3\,H_2O + N_2O$

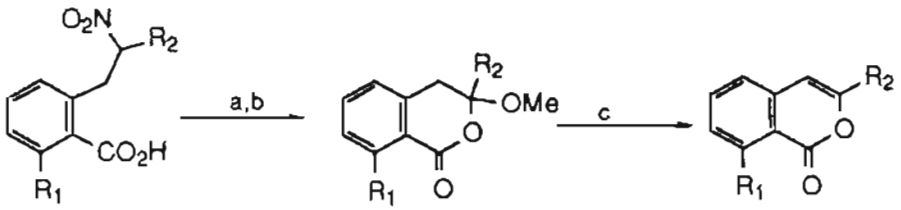
the nitroalkane **371**. With strong acid, the *aci*-nitroalkane **374** is protonated to give the intermediate **375**. Water adds across the carbon-nitrogen double bond to initially give the protonated species **376** which loses a proton to water to yield the hydroxylic intermediate **377**. At this point, the pathway splits into two directions. In path B, protonation on the nitrogen yields **381**, which in a slow step loses $HN(OH)_2$ to form the carbonyl compound **366**. In path A, loss of water from the hydroxylated nitrogen in **377** yields a hydroxynitroso intermediate **378**, which is believed to give rise to the blue color. Protonation of the nitroso group in **378** gives **379**, which in a slow step loses HON to yield the protonated carbonyl **380**. Proton transfer to water results in the transformation of **380** into the carbonyl **366**. In both pathways the final products are the carbonyl compound and nitrous oxide.

The mechanism takes into account the inverse effect of water on the reaction, since through path A, water is produced through an equilibrium step prior to the slow step in the reaction. Furthermore, this hypothesis is reasonable since pathway A produces a nitroso compound and it has been shown that hydrolysis of α-chloronitroso compounds produces ketones in quantitative yield.

The Nef reaction has been found to give poor results at times, and this has been traced to the low solubility of organic substrates in aqueous media. A modified Nef reaction has been developed by Jacobson[143], utilizing methanol as the solvent. Generation of the nitro anion of **360b** with sodium methoxide in methanol followed by its addition to a solution of sulfuric acid in methanol produced a beautiful blue solution. The

isolated product was presumably the carboxy ketal **362b** schown in Scheme 3.21. Treatment of this material with perchloric acid and acetic anhydride in refluxing ethyl acetate[135] furnished 3-methylisocoumarin **363b** in 84% yield. The procedure also worked well if the nitro anion was generated in aqueous sodium hydroxide or in a solution of aqueous sodium hydroxide and methanol. Application of this procedure to the other nitro acids **360b,c,d,f** gave the isocoumarins **363b,c,d,f** in 79-85% yield. With the exception of **361a** the procedure worked well. The experimental conditions, though acidic, were much simpler than the McMurry method. Workup and isolation was straightforward and the products were readily isolated in pure form.

Scheme 3.21



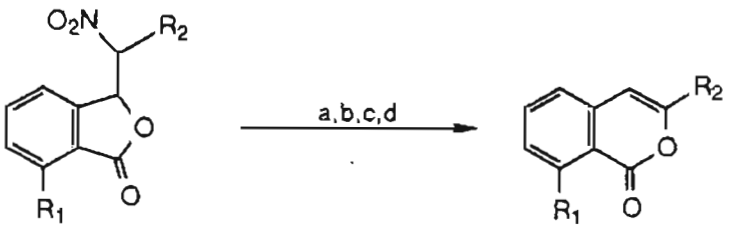
360 **362** **363**

a. NaOH, H_2O, MeOH b. H_2SO_4, MeOH c. $HClO_4$, Ac_2O, EtOAc

	R_1	R_2	% yield
a	H	H	-
b	H	Me	84
c	H	Et	85
d	H	Ph	84
f	OMe	PhOMe	79

A modification of the above procedure allowing the preparation of isocoumarins in just two steps is shown in Scheme 3.20. Instead of isolating the sodium borohydride reduction products **360b,c,e**, aqueous sodium hydroxide was added to the dimethyl sulfoxide solution of the nitro acid to ensure anion formation. The anion solution was then slowly added to sulfuric acid in methanol at 0 °C. The reaction turned to a sky blue color, which persisted for 1-2 hours. Once the blue color disappeared, the Nef product was extracted with ethyl acetate. Treatment of an ethyl acetate solution of this intermediate with perchloric acid and acetic anhydride at reflux for 1-2 hours gave the isocoumarins (**363b,c,e**) in 65-85% yield. The abbreviated sequence produced higher yields, was more efficient, and allowed for 3 steps to be performed without purification of intermediates.

Scheme 3.22



359 **363**

a. $NaBH_4$, DMSO b. NaOH, H_2O
c. H_2SO_4, MeOH d. $HClO_4$, Ac_2O, EtOAc

	R_1	R_2	% yield
b	H	Me	68
c	H	Et	85
e	OMe	Me	67

The developed sequence constitutes a new and reasonably efficient method for synthesis of isocoumarins from phthalaldehydic acid and nitro compounds. By employing this sequence, it was possible to prepare the isocoumarins in only two steps. The experimental conditions were indeed generally mild. The nitro-aldol condensation with triethylamine is extremely mild and efficient. The Nef reaction is admittedly limited to acid stable substrates, but other than that, no other severe conditions were required.

As noted earlier, the recent report by Staunton allowed for efficient preparation of methoxy substituted isocoumarins.[130] However, that method was limited to the preparation of isocoumarins containing a methoxyl group at C-7. This was due to the fact that anions of unsubstituted *ortho*-toluates are very reactive and readily undergo side reactions. The presences of a C-6 methoxy group on the toluate is required to stabilize the anion and prevent self condensation from taking place at the ester functionality.[103] Our procedure is versatile allowing for preparation of isocoumarins with or without a C-7 methoxy group. The methodology is straightforward and the yields are generally good.

Part IV: PHENYLNITROMETHANES

I. Introduction

In conjunction with the isocoumarin work, we needed a variety of phenylnitromethanes with a methoxylated aromatic ring. The lack of precedent and apparent synthetic limitations of the previously reported methods led us to explore the preparation of phenylnitromethanes.

The reaction of benzyl halides with silver nitrite[140] and the base induced alkylation of phenylacetonitriles with alkyl nitrates[141] are the only two methods that have been reported for the preparation of phenylnitromethanes, and neither has been demonstrated to be of general synthetic utility for the preparation of ring methoxylated analogs. For example, Kornblum and coworkers[140c] observed that while benzyl bromide reacts with silver nitrite to give phenylnitromethane, corresponding reaction of *para*-methoxybenzyl bromide gives predominantly the nitrite ester (55%). The alkylation of phenylacetonitrile with alkyl nitrates, a two step procedure in which the α-nitrophenylacetonitrile from the initial condensation is first isolated, then hydrolyzed and decarboxylated,[141] has not been used for the preparation of methoxyphenylnitromethanes.

Although it has been shown that dianions of aliphatic acids react with alkyl nitrates to give nitroparaffins,[142] the preparation of phenylnitromethanes was not investigated.

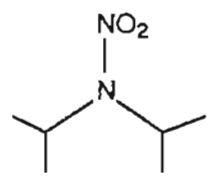
II. Synthesis

We explored the preparation of phenylnitromethanes through nitration of the dianions of phenylacetic acid with methynitrate,[143] as shown in Scheme 4.1. Initially, the phenylacetic acids **382** were reacted with three equivalents of LDA at -78 °C, then quenched with three equivalents of methyl nitrate and acidified. The product mixture was separated by chromatography furnishing the desired phenylnitro-

Scheme 4.1

382 **383**

	R_1	R_2	R_3	R_4	% Yield
a	H	H	H	H	72
b	OMe	H	H	H	83
c	H	OMe	H	H	72
d	H	H	OMe	H	77
e	H	OMe	OMe	H	63
f	OMe	H	H	OMe	70



384

methane **383** and diisopropylnitramine **384**. The latter material was shown to arise from reaction of the excess LDA and methyl nitrate. Reducing the relative stoichiometry of LDA to acid to 2.2:1 minimized formation of the nitramine by-product. This obviated the need for chromatographic separation and permitted, in most instances, direct isolation of product phenylnitromethanes through crystallization and/or distillation.

In initial work on the reaction, we observed that while 2-methoxy- and 2,5-dimethoxyphenylacetic acid gave clear solutions of the dianions, the remaining acids gave suspensions. It has been noted previously that addition of HMPA to dianion suspensions effects their dissolution and gives improved yields on subsequent reaction with electrophiles. Generation of phenylacetic acid dianions in the presence of added HMPA gave homogenous solutions, which on reaction with methyl nitrate and subsequent acidification, gave the best yields of phenylnitromethanes. Irrespective of the presence of HMPA, nearly identical yields of phenyl-nitromethanes were obtained from dianions of acids that initially give homogeneous solutions.

In summary, condensation of the dianions of ring methoxylated phenylacetic acids with methyl nitrates provides a general, one step, procedure to the corresponding phenylnitromethanes in good to very good yield.

Summary

Synthesis of 7,9-dideoxydaunomycinone (**56**) from an 11-deoxy-daunomycinone precursor demonstrated the feasibility of preparing both compounds from a common intermediate. The convergent sequence is brief and efficient, producing gram quantities of **56** in seven steps from 3-phenylsulfonyl-7-methoxy-1(3H)-isobenzofuranone and 6-acetyl-4a,5,6,7,8,8a-hexahydro-1(4H)-naphthalenone (**115**) in 15% overall yield.

In conjunction with the above daunomycinone synthesis, a new and convenient preparation of **115** from (*1*)-perilaldehyde was developed. The new route to **115** was efficient and experimentally non-tedious permitting moderate scale preparation of **115**. An added feature of this procedure was that all of the intermediates and even the final product could be purified by distillation.

Several approaches to pillaromycinone were examined. Attempts to prepare the cyclohexadienyl Michael acceptor **201** were stymied by the instability of the diene moiety. Other attempts to prepare either the dithioketal Michael acceptor **235** or the lactone Michael acceptor **246** were also unsuccessful. The cyclopentenyl Michael acceptor **255** was prepared from 2-cyclopenteneacetic acid. Michael condensation of ethyl 2-phenylsulfinylmethylbenzoate (**200**) with 4-(2-cyclopentenyl)-2-butenoate gave the naphthalene **259** in modest yield. However, use of the

Ene reaction to converted the aldehyde **261** into the tetracyclic intermediate **262** was unsuccessful. The Michael acceptor, methyl 4-(3-oxocyclopentyl)-3-butenoate ethylene acetal (**277**), was then prepared from 2-cyclopentenone. Michael condensation of **200** with **277** furnished the naphthalene intermediate **279b**. Aldol cyclization of the keto aldehyde **281** gave the tetracyclic ketone **282**. *Cis*-hydroxylation of the double bond in **287**, and reoxidation to the ketone yielded 3a,4-dihydroxy-5,6-dimethoxy-2,3,3a,4,11,11a-hexahydro-3(1H)-cyclopenta[b]anthracenone (**290**) protected as the acetonide. The aldol reaction proved to be successful for the formation of the tetracyclic intermediate **282**. Although the double bond in **282** was resistant to hydroxylation, the problem was remedied by reduction of the ketone in **282** to an alcohol prior to hydroxylation.

An efficient general method for the preparation of 1(H)-2-benzopyran-1-ones through condensation of *ortho*-carboxybenzaldehydes (**357**) with various nitroalkanes was developed. The overall yields were good and the preparations were accomplished under mild conditions. In the future, the use of 1(H)-2-benzopyran-1-ones for preparation of substituted naphthalenes would enable further work on the synthesis of pillaromycinone.

Experimental Procedures

General. Melting points were taken on a Kofler hot-stage microscope and are uncorrected. IR spectra were recorded on a Perkin-Elmer 621 or FT-1800 spectrophotometer and are expressed in wavenumbers. Proton and ^{13}C NMR spectra were recorded on a JEOL FX90Q spectrometer. Chemical shifts were reported as δ values in ppm relative to TMS. Mass spectra were obtained with a DuPont 21-491B or a VG 7070E spectrometer at an ionizing voltage of 70 eV. Analytical thin layer chromatography plates (silica gel 60 F-254, layer thickness 0.25mm) were manufactured by E. Merck and Co. Silica gel for column chromatography utilized E. Merck silica gel 60, 70-230 mesh ASTM. Florisil for column chromatography was from Fisher Scientific (100-200) mesh. Radial thick layer chromatography was performed on a Chromatotron (Harrison Research) with plates (2 and 4 mm thickness) made with silica gel from E. Merck (60, PF-254). Carbon, hydrogen, and nitrogen analyses were performed by Galbraith Laboratories, Knoxville, Tennessee.

Tetrahydrofuran (THF) and dimethoxyethane (DME) were distilled from lithium aluminum hydride. Triethylamine, diisopropylamine, hexamethylphosphoramide (HMPA), CH_2Cl_2, CCl_4, and dimethyl sulfoxide (DMSO) were distilled from CaH_2. Methyl ethyl ketone (MEK) was dried over $MgSO_4$, filtered, and the residual moisture was azeotropically distilled. Pyridine was distilled from BaO. Hexanes, CH_2Cl_2, and ethyl acetate (EtOAc), for chromatographic purposes were distilled. Allyl bromide was distilled prior to use. All other reagents were not purified.

I. Daunomycinone

9,10-Dihydroxy-2,3-dihydro-1(4H)-anthracenone (120a). Powdered phthalide sulfone **118** (10.0 g, 36.0 mmol) was added to a magnetically stirred cold (-70 °C) solution of lithium *t*-butoxide (79.0 mmol) prepared from *n*-BuLi (2.2 M, 36.0 mL, 79.0 mmol) and *t*-BuOH (7.4 mL, 79.0 mmol)) in dry THF (500 mL). The resulting yellow anion solution was stirred for 15 min and then 2-cyclohexenone (4.3 mL, 44.0 mmol) was added and the reaction was stirred a further 15 min, during which time the solution turned red. The ice bath was removed and the reaction, while stirring, was allowed to come to room temp and react for 2 hr. Hydrochloric acid (6 M, 20 mL) was added and the resultant yellow solution was concentrated under reduced pressure. The residue was dissolved in ether (200 mL) and washed with aqueous sodium bicarbonate (70 mL), water (70 mL), and brine (40 mL), then dried ($MgSO_4$), filtered, and evaporated at reduced pressure. The residue was recrystallized from ethanol and water to yield 5.5 g (66%) of **120a** as a yellow orange powder with mp 195-196 °C (ether-hexanes). ^{1}H-NMR ($CDCl_3$) δ 2.14 (tt, 2H, J = 7 Hz, C$\underline{H}_2$), 2.74 (t, 2H, J = 7 Hz, ArC$\underline{H}_2$), 2.86 (t, 2H, J = 7 Hz, ArCOC$\underline{H}_2$), 4.61 (s, 1H, ArO$\underline{H}$), 7.4-7.8 (m, 2H, Ar$\underline{H}$), 8.04 (dd, 1H, J = 8 Hz, J = 2 Hz, Ar$\underline{H}$), 8.42 (dd, 2H, J = 8 Hz, J = 2 Hz, Ar$\underline{H}$), 13.8 (s, 1H, H-bonded ArO$\underline{H}$).

9,10-Dimethoxy-2,3-dihydro-1(4H)-anthracenone (120b). Anhydrous potassium carbonate (11 g, 79 mmol) and dimethyl sulfate (3.7 mL, 39 mmol) were added to **120a** (3.0 g, 13 mmol) dissolved in dry methyl ethyl ketone (180 mL). The magnetically stirred mixture was heated at reflux for 2 days. The reaction was cooled, then filtered, and the filtered cake washed with hot methyl ethyl ketone (100 mL). Triethylamine (15 mL) was added to the filtrate and the solution was stirred several hours to destroy excess dimethyl sulfate. The solvent was evaporated at reduced pressure and the residue was taken up in ethyl acetate (100 mL), washed with water (3 x 50 mL), then dried ($MgSO_4$), filtered, and evaporated at reduced pressure. Recrystallization of the yellow residue from ether-hexanes gave 2.14 g (63%) of pure **120b** with mp 116-118 °C. ^{1}H-NMR ($CDCl_3$) δ 2.10 (tt, 2H, J = 7 Hz, $C\underline{H}_2$), 2.72 (t, 2H, J = 7 Hz, $ArC\underline{H}_2$), 3.12 (t, 2H, J = 7 Hz, $ArCOC\underline{H}_2$), 3.90 (s, 3H, $OC\underline{H}_3$), 4.00 (s, 3H, $OC\underline{H}_3$), 7.4-7.7 (m, 2H, Ar$\underline{H}$), 8.0-8.2 (m, 1H, Ar$\underline{H}$), 8.2-8.4 (m, 1H, Ar$\underline{H}$).

4-Hydroxy-9,10-dimethoxy-2,3-dihydro-1(4H)-anthracenone (121b). To the dimethyl ether **120b** (2.4 g, 9.4 mmol) dissolved in dry boiling carbon tetrachloride (1 L) under a nitrogen atmosphere was added N-bromosuccinimide (2.0 g, 11.3 mmol) and the mixture heated at reflux under illumination (sunlamp 275 W) for exactly 20 min. The reaction was immediately chilled in an ice bath and the precipitated succinimide was filtered. The solvent was evaporated under reduced pressure (bath < 40 °C) and the dark residue was redissolved in THF (100 mL) containing water (100 mL) and stirred at room temperature.

for 1 hr. Solid $NaHCO_3$ (4 g) was added to the solution which was then extracted with ethyl acetate (4 x 50 mL). The combined organic phases were washed with water (100 mL) and brine (50 mL), then dried ($MgSO_4$), filtered, and evaporated under reduced pressure. Chromatography of the residue on florisil (50 g, 1:1 hexanes-CH_2Cl_2) yielded 1.7 g (65%) of pure **121b** with mp 124-126 °C (recrystallized from CH_2Cl_2-hexanes). ^{1}H-NMR ($CDCl_3$) δ 2.0-3.2 (m, 4H, -C<u>H</u>$_2$-), 3.34 (brd s, 1H, O<u>H</u>), 3.95, 3.97 (s, 6H-combined, OC<u>H</u>$_3$), 5.47 (brd s, 1H, ArC<u>H</u>OH), 7.4-7.7 (m, 2H, Ar<u>H</u>), 7.9-8.1 (m, 1H, Ar<u>H</u>), 8.3-8.1 (m, 1H, Ar<u>H</u>).

9,10-Dimethoxy-2,3-dihydroanthracene-1,4-dione (123). To a solution of Collins reagent prepared from pyridine (9.5 mL, 118 mmol) and CrO_3 (5.9 g, 59 mmol) in dry methylene chloride (130 mL) was added in one portion a solution of **121b** (1.54 g, 5.7 mmol) in methylene chloride (23 mL). The reaction was stirred for half hour at room temperature under nitrogen. Ether (50 mL) was added to the reaction and the mixture was filtered through Celite to remove chromium salts. The filtrate was washed with water (75 mL) and brine, then dried ($MgSO_4$), filtered and evaporated at reduced pressure. The residue was recrystallized (ether-hexanes) to give 1.02 g (67%) of **123** as orange-yellow needles with mp 137-140 °C. ^{1}H-NMR ($CDCl_3$) δ 3.06 (s, 4H, -C<u>H</u>$_2$), 4.06 (s, 6H, OC<u>H</u>$_3$), 7.6-7.8 (m, 2H, Ar<u>H</u>), 8.3-8.5 (m, 2H, Ar<u>H</u>); mass spectrum, *m/z* 270 (M^+).

9,10-Dimethoxy-1,4-anthraquinone (124). To a solution of the diketone **123** (300 mg, 1.1 mmol) in methylene chloride (10 mL) and dioxane (10 mL) was added selenium dioxide (246 mg, 2.2 mmol). The reaction was heated at reflux for 2 hr, then cooled to room temperature. Aqueous hydrochloric acid (30 mL, 4 N) and ether (60 mL) were added. The mixture was filtered and the layers were separated. The aqueous layer was extracted with additional ether (2 x 50 mL), and the combined ether extracts were washed with water (50 mL) and brine, then dried ($MgSO_4$), filtered and evaporated at reduced pressure. The residue was recrystallized (MeOH) to yield 270 mg (90%) of **124** as orange crystals with mp 192-195 °C. ^{1}H-NMR ($CDCl_3$) δ 4.06 (s, 6H, OCH_3), 6.89 (s, 2H, vinyl H), 7.7- 7.9 (m, 2H, ArH), 8.3-8.5 (m, 2H, ArH).

Anal. Calcd. for $C_{16}H_{12}O_4$: C, 71.63; H, 4.51. Found: C, 71.60; H, 4.55.

1-(1-Hydroxy-3-butenyl)-4-(1-methylethenyl)-1-cyclohexene (126). Allyl magnesium bromide was prepared by dropwise addition of a solution of allyl bromide (22.8 mL, 0.264 mol) and 1,2-dibromoethane (13.6 mL, 0.160 mol) in ether (50 mL) to a chilled (0 °C) magnetically stirred mixture of Mg turnings (115.3 g, 0.640 mol) in anhydrous ether (200 mL) under a nitrogen atmosphere. To ensure that the Grignard reagent had completely formed, the reaction was stirred an additional 2 hr. (*l*)-Perillaldehyde (**125**, 25 g, 0.150 mol) in ether (50 mL) was added dropwise over 1 hr. to the still chilled Grignard reagent, then stirred overnight. The excess Mg was filtered off using a Buchner funnel with no filter paper and the resulting solution was quenched by addition

of excess aqueous ammonium chloride (400 mL). The layers were separated and the aqueous phase was further extracted with ether (2 x 200 mL). The combined organic layers were successively washed with aqueous ammonium chloride (200 mL), aqueous bicarbonate (200 mL), water (200 mL), and brine. Evaporation of the ether at reduced pressure and distillation of the residue gave 30 g (93%) of **126** as a light yellow oil with bp 102 ^{o}C/ 1.5 mm and was unresolvable by TLC. ^{1}H-NMR ($CDCl_3$) δ 1.0-2.4 (m, 10H, 7 allylic H, 1-CH_2, ROH), 1.73 (s, 3H, CH_3), 4.03 (t, 1H, J = 8 Hz, -CHOH-), 4.71 (brd s, 2H, vinyl H), 5.00-5.30 (m, 2H, vinyl H), 5.5-6.0 (m, 2H, vinyl H); mass spectrum, *m/z* 192 (M^+); IR (film) cm^{-1} 3400 (O-H), 3080 (vinyl C-H), 1640 (C=C), 990, 910, 880.

2-(2-Propenyl)-4-(1-methylethenyl)cyclohexane-carboxaldehyde (127). Potassium hydride in oil (227g, 35%, 1.70 mol) was washed successively with dry hexanes (3 x 200 mL) and once with dry DME (200 mL) to remove the oil, then suspended in dry DME (1 - 1.5 l) with magnetic stirring under a nitrogen atmosphere. A solution of the alcohol **126** (95.6 g, 0.498 mol) in DME (100 mL) was slowly added dropwise to the hydride suspension so as to maintain a moderate rate of hydrogen evolution. Once the addition was completed, the mixture was stirred for 0.5 hr at room temperature to ensure anion formation. The orange-red solution was heated at reflux for 48 hr, and during this period the solution turned dark red. The reaction was cooled to room temperature and the excess potassium hydride decomposed by dropwise addition of isopropyl alcohol (160 mL). Addition of glacial acetic acid (120 mL) to

neutralize the reaction produced a precipitate which dissolved on addition of water (200 mL). The layers were separated and the aqueous phase was further extracted with ethyl acetate (2 x 200 mL). The combined organic solutions were evaporated at reduced pressure and the resultant oil was taken up in ether (800 mL) and washed successively with aqueous bicarbonate (2 x 200 mL) and brine (200 mL), then dried ($MgSO_4$), filtered, and evaporated at reduced pressure. Distillation of the residue gave 70 g (73%) of **127** as a light yellow oil with bp 90-95 °C / 3 mm. The ^{1}H-NMR spectrum and analysis of the TLC showed that the product was a 1:1 mixture of isomeric aldehydes. ^{1}H-NMR ($CDCl_3$) δ 1.1-2.6 (m, 11H, 3 allylic H, 3-CH_2, 1-CH, CHCOR), 1.67, 1.71 (s, 3H-combined, CH_3), 4.69 (brd s, 2H, vinyl H), 4.80-5.20 (m, 2H, vinyl H), 5.3-6.0 (m, 1H, vinyl H), 9.67, 9.71 (s, 1H-combined, aldehyde CHO); IR (film) cm^{-1} 3080 (vinyl C-H), 2700 (aliphatic C-H), 1730 (C=O), 1645 (C=C), 995, 910, 885.

Anal. Calcd. for $C_{13}H_{20}O$: C, 81.20; H, 10.48. Found: C, 81.31; H, 10.32.

1-Acetyl-4-(1-methylethenyl)-2-(2-propenyl)-cyclohexane (128b). A solution of **127** (70 g, 0.365 mol) in ether (200 mL) was added dropwise over 1 hr to a chilled (-10-0 °C), magnetically stirred solution of MeLi (316 mL, 1.5 M, 0.474 mol) in anhydrous ether (200 mL) under a nitrogen atmosphere. The reaction was heated at reflux for 10 min and then quenched by slow addition of water (200 mL) and glacial acetic acid (30 mL). The layers were separated and the organic phase was washed with water (2 x 200 mL), aqueous bicarbonate (100 mL) and brine, then dried ($MgSO_4$), filtered, and

evaporated at reduced pressure to give 74.3 g (98%) of **128a** which was used in the next step without purification. A TLC analysis of the product showed two spots. ^{1}H-NMR ($CDCl_3$) δ 1.8-2.4 (m, 12H, 3 allylic H, 3 -CH_2, 2-CH, ROH), 1.25 (s, 3H, CH_3), 1.69 (s, 3H, CH_3), 3.3-4.3 (m, 1H, CHOH), 4.68 (brd s, 2H, vinyl H), 4.90-5.15 (m, 2H, vinyl H), 5.3-5.9 (m, 1H, vinyl H); IR (film) cm^{-1} 3380 (O-H), 3080 (vinyl C-H), 1645 (C=C), 990, 905, 890.

A solution of dimethyl sulfoxide (40.8 mL, 0.577 mol) in methylene chloride (100 mL) was added over 20 min to a chilled (-60 °C) magnetically stirred solution of oxalyl chloride (25.3 mL, 0.288 mol) in dry methylene chloride (500 mL) under a nitrogen atmosphere. The above alcohol **128a** (30.0 g, 0.144 mol) in methylene chloride (200 mL) was added slowly over a 25 min period to the chilled DMSO-oxalyl chloride solution. The solution was stirred for an additional 25 min, then triethylamine (120 mL) was added in a thin stream to the reaction which produced a precipitate. After an additional 15 min, the reaction was warmed to room temp and the precipitate dissolved. Water (150 mL) was added and the layers were separated. The aqueous phase was further extracted with methylene chloride (2 x 200 mL) and the combined organic layers were washed with aqueous bicarbonate (100 mL) and brine, then dried ($MgSO_4$), filtered, and evaporated at reduced pressure. Distillation of the residue at reduced pressure gave 24.6 g (82%) of **128b** as a light yellow oil with bp 90-100 °C / 2 mm. The ^{1}H-NMR spectrum and TLC analysis showed that the product was a mixture of isomeric ketones. ^{1}H-NMR ($CDCl_3$) δ 1.0-2.4 (m, 11H, 3 allylic H, 3-CH_2-, 2-CH), 1.60, 1.70 (s, 3H-combined, CH_3), 2.10, 2.14 (s, 3H-combined, $COCH_3$), 4.68 (brd s, 2H, vinyl H), 4.84-5.26 (m, 2H, vinyl H),

5.4-5.9 (m, 1H, vinyl H); IR (film) cm^{-1} 3080 (vinyl C-H), 1715 (C=O), 1645 (C=C), 990, 912, 890; mass spectrum, *m/z* 206 (M^+)

1,4-Diacetyl-2-(2,2-dimethoxyethyl)cyclohexane (129a). Ozone was bubbled through a cold (-70 °C) solution of **128b** (29.1 g, 0.141 mol) in methanol until the blue color of ozone persisted (3.5 hr). Oxygen and then nitrogen were bubbled through the reaction solution until the blue color dissappeared. Dimethyl sulfide (100 mL) was added to the cold reaction solution and the mixture was allowed to warm to room temperature and stirred overnight. When a starch-iodide test was negative, nitrogen was bubbled through the solution to remove excess dimethyl sulfide. The solution was concentrated at reduced pressure at room temperature to a fourth of the original volume, then diluted with ethyl acetate (200 mL) and brine (100 mL). The ethyl acetate layer was separated, dried (Na_2SO_4), filtered, and evaporated at reduced pressure to yield 33.7 g (94%) of the dimethyl acetal **129a**. The product, though unresolvable by TLC, was an isomeric mixture by NMR and was used in the next step without without purification. ^{1}H-NMR ($CDCl_3$) δ 1.2-2.6 (m, 11H, 4-C$\underline{H}_2$, 3-C$\underline{H}$), 2.11, 2.15 (s, 6H-combined, COC$\underline{H}_3$), 3.21, 3.31, 3.48 (s, 6H-combined, OC$\underline{H}_3$), 4.2-4.6 (m, 1H, C$\underline{H}$(OCH_3)$_2$); IR (film) cm^{-1} 1700 (C=O); mass spectrum, *m/z* 226 (M^+-OCH_3).

6-Acetyl-4a,5,6,7,8,8a-hexahydro-1(4H)-naphthalenone (115). Two procedures were employed to transform **129a** to **115**. ***Method A***: A solution of the dimethylacetal **129a** (14.1 g, 55 mmol) in

THF (180 mL) and aqueous hydrochloric acid (6 N, 80 mL) was stirred at room temperature for 0.5 hr, during which time the mixture turned a green color. The reaction was warmed on a steam bath for 20 min, then NaCl (solid, excess) and ether (80 mL) were added. The mixture was stirred with heating for 30 min and then at room temperature for another 40 min. The layers were separated and the aqueous phase was again extracted with ether (500 mL). The combined ether solutions were washed with aqueous bicarbonate (200 mL) and brine (75 mL), then dried ($MgSO_4$), filtered, and evaporated at reduced pressure. Chromatography of the residue on silica gel (100 g, benzene) gave 5.6 g (53%) of **115** as a mixture of isomers which solidified on standing. This material exhibited TLC behavior and had a ^{1}H-NMR spectrum identical to an alternatively prepared sample of **115**.

Method B: The dimethyl acetal **129a** (28.7 g, 112.0 mmol) dissolved in a mixture of THF (50 mL) and hydrochloric acid (1N, 60 mL) was stirred at room temp for 2 hr. Solid sodium bicarbonate (excess) was added and the mixture extracted with ethyl acetate (2 x 100 mL). The combined organic extracts were washed successively with water (100 mL), aqueous bicarbonate (100 mL), and brine, then dried ($MgSO_4$), filtered, and evaporated at reduced pressure to give 25.5 g of **129b**. ^{1}H-NMR ($CDCl_3$) δ 2.7-1.0 (m, 17H, 2-C$\underline{H}_3$, 4-C$\underline{H}_2$, 3-C$\underline{H}$), 9.71 (s, 1H, aldehyde C$\underline{H}$O).

An anhydrous ether solution of hydrochloric acid (0.97 N, 110 mL) was added to a magnetically stirred solution of the above aldehyde **129b** in anhydrous ether (325 mL) under a nitrogen atmosphere. The mixture

was stirred at room temp for 20 hr, then aqueous bicarbonate (100 mL) was added and the layers separated. The ether solution was washed with water (200 mL), then dried ($MgSO_4$), filtered, and evaporated at reduced pressure to give 23.8 g of a dark oil. A ^{1}H-NMR spectrum of this material showed the presence of the enone **115.** A multiplet (δ 4.05) in the ^{1}H NMR spectrum indicated some hydrogen chloride addition product **130** was present. In order to convert this secondary material to the naphthalenone **115,** the crude product was dissolved in benzene (200 mL) containing triethylamine (15 mL). The solution was heated at reflux for 2.5 hr, then cooled. The benzene solution was washed with water (200 mL), hydrochloric acid (2N, 200 mL), water (200 mL), and KOH (1 N, 100 mL), then dried ($MgSO_4$), filtered, and evaporated at reduced pressure. Elution of the residue through a small amount of silica gel (10 g, EtOAc) yielded 23.0 g of a viscous oil which was extracted with hot hexanes (liquid-liquid extractor). Evaporation of hexanes under vacuum gave 18.5 g (64% from the acetal) of **115** which crystallized upon standing. Two recrystallizations of the material from hexanes gave the product with mp 94-99 °C. A more expedient procedure for the purification of **115** was to distill (bp 120 °C / 0.8 mm) the material from the initial chromatography. ^{1}H-NMR ($CDCl_3$) δ 1.10-2.60 (m, 11H, 2 allylic H, 3-CH_2, 3-CH), 2.16 (s, 3H, CH_3), 5.80-6.10 (m, 1H, α vinyl H), 6.80-7.08 (m, 1H, β vinyl H); ^{13}C-NMR ($CDCl_3$) δ 24.6, 27.6, 27.8, 33.2, 34.5, 39.9, 50.0, 129.3 (α vinyl C ?), 148.4 (β vinyl C?), 199.9 (conjugated C=O), 210.6 (isolated C=O); mass spectrum, *m/z* 192 (M^+). The TLC behavior, IR, ^{1}H- and ^{13}C-NMR spectra were identical with that of an alternatively prepared sample.

9-Acetyl-5,12-dihydroxy-4-methoxy-6a,7,8,9,10,10a-hexahydro-6(11H)-naphthacenone (116). The powdered phthalide sulfone **103** (10.0 g, 32.9 mmol) was added to a magnetically stirred cold (-70° C) solution of lithium *t*-butoxide (98.7 mmol) prepared from *n*-BuLi (2.1 M, 47.0 mL, 98.7 mmol) and *t*-BuOH (9.6 mL, 102 mmol) in dry THF (100 mL). The resulting yellow anion solution was stirred for 15 min and then powdered **115** (6.63 g, 34.5 mmol) was added. The reaction was stirred for 15 min, during which time the solution turned red. The ice bath was removed and the reaction, while stirring, was allowed to come to room temp and react for 2 hr. Hydrochloric acid (4 M, 25 mL, 100 mmol) was added and the resultant yellow solution was concentrated under reduced pressure to one-half volume. The precipitated product was filtered off and transferred into boiling acetone (250 mL). The solution was cooled, then filtered to yield 9.0 g (77%) of **116** as a yellow powder with mp 223-227 °C. ^{1}H-NMR (1.5% CF_3CO_2H-$CDCl_3$) δ 1.2-3.5 (m, 11H, benzylic-C<u>H</u>$_2$, 3-C<u>H</u>$_2$, 3-C<u>H</u>), 2.31 (s, 3H, C<u>H</u>$_3$), 4.03 (s, 3H, OC<u>H</u>$_3$), 6.94 (dd, 1H, J = 8 Hz, J = 2 Hz, Ar<u>H</u>), 7.4-7.8 (m, 2H, Ar<u>H</u>); mass spectrum, *m/z* 354 (M^+).

9-Acetyl-4,5,12-trimethoxy-6a,7,8,9,10,10a-hexahydro-6-(11H)-naphthacenone (131a). Anhydrous potassium carbonate (87 g, 630 mmol) and dimethyl sulfate (48 mL, 50.5 mmol) were added to **116** (9.0 g, 25.4 mmol) dissolved in dry methyl ethyl ketone (1 L). The mechanically stirred mixture was heated at refluxed for 2 days. The reaction mixture was cooled, filtered, and the filter cake washed with hot

methyl ethyl ketone (700 mL). Triethylamine (100 mL) was added to the filtrate and the solution was stirred several hours to destroy excess dimethyl sulfate. The solvent was evaporated at reduced pressure and the residue was taken up in ethyl acetate (900 mL) and washed with water (3 x 500 mL), then dried ($MgSO_4$), filtered, and evaporated at reduced pressure. Repeated recrystallization of the yellow residue from ethyl acetate-hexanes gave 6.14 g (63%) of pure **131a** with mp 178-180 °C. Chromatography of the combined filtrates from the recrystallization on silica gel (100 g, 10-20% EtOAc-hexanes) furnished 2.25 g (23%; 88% overall) of **131a** as a mixture of isomers. Brief treatment of a sample of this mixture with alcoholic sodium hydroxide gave a single product with TLC behavior, ^{1}H-NMR spectrum and mp identical with the major isomer. ^{1}H-NMR ($CDCl_3$) δ 1.3-3.6 (m, 11H, benzylic-C$\underline{H}_2$, 3-C$\underline{H}_2$, 3-C$\underline{H}$), 2.20 (s, 3H, COC$\underline{H}_3$), 3.85 (s, 3H, OC$\underline{H}_3$), 3.91 (s, 3H, OC$\underline{H}_3$), 3.99 (s, 3H, OC$\underline{H}_3$), 6.86 (d, 1H, J = 8 Hz, Ar$\underline{H}$), 7.4-7.7 (m, 2H, Ar$\underline{H}$); mass spectrum, *m/z* 382 (M^+).

9-Acetyl-11-hydroxy-4,5,12-trimethoxy-6a,7,8,9,10,10a-hexahydro-6(11H)-naphthacenone (131c). To **131a** (4.0 g, 10.5 mmol) dissolved in hot dry carbon tetrachloride (1.3 L) was added N-bromosuccinimide (2.3 g, 12.6 mmol). The mixture was magnetically stirred and heated at reflux under illumination (275 W sunlamp) for exactly 20 min, then immediately chilled in an ice bath. The precipitated succinimide was filtered off and the filtrate was evaporated at reduced pressure (bath < 40 °C). The residue was taken up in THF (300 mL) and water (300 mL) and stirred at room temperature for 2.5 hr. The

reaction solution was concentrated under reduced pressure to 2/3 volume. Aqueous bicarbonate (50 mL) was added and the mixture was extracted with ethyl acetate (3 x 150 mL). The combined ethyl acetate extracts were washed with water (100 mL) and brine, then dried (Na_2SO_4), filtered, and evaporated at reduced pressure. Chromatography of the residue on florisil (100 g, 10% EtOAc-CH_2Cl_2 followed by MeOH) yielded 2.68 g (64%) of nearly pure **131c**, which after recrystallization (CH_2Cl_2-CCl_4), had mp 123-125 °C. ^{1}H-NMR ($CDCl_3$) δ 1.5-3.3 (m, 10H, 3-C$\underline{H}_2$, 3-C$\underline{H}$, RO$\underline{H}$), 2.14, 2.21 (s, 3H-combined, COC$\underline{H}_3$), 3.84, 3.86, 3.97 (s, 9H-combined, OC$\underline{H}_3$), 5.14 (brd s, 1H, ArC$\underline{H}$OH), 6.84 (d, 1H, J = 9 Hz, Ar$\underline{H}$), 7.3-7.7 (m, 2H, Ar$\underline{H}$); mass spectrum, *m/z* 398 (M^+).

9-Acetyl-4,5,12-trimethoxy-6a,7,8,9,10,10a-hexahydronaphthacene-6,11-dione (132). The alcohol **131c** (5.15 g, 12.9 mmol) in methylene chloride (50 mL) was added in one portion to a magnetically stirred solution of Collins reagent prepared from pyridine (42 mL, 0.52 mol), and CrO_3 (15.5 g, 0.155 mol) in methylene chloride (400 mL). The reaction was stirred at room temp for 1 hr, then decanted and the methylene chloride solution evaporated. Both the residues from the reaction and the evaporation were extracted with hot ethyl acetate (3 x 200 mL) and the ethyl acetate extracts were filtered. The combined ethyl acetate solutions were washed with aqueous bicarbonate (2 x 100 mL), water (200 mL) and brine (75 mL), then dried ($MgSO_4$), filtered and evaporated at reduced pressure to give 2.75 g (54%) of **132** as a 1:1 mixture of isomers which was used in the next step without further purification.

^{1}H-NMR ($CDCl_3$) δ 2.3-1.4 (m, 9H, 3-C$\underline{H}_2$, 3-C$\underline{H}$), 2.21, 2.14 (s, 3H-combined, CO$\underline{CH}_3$), 4.02, 3.99, 3.97, 3.95 (s, 9H-combined, O$\underline{CH}_3$), 7.06 (d, 1H, J = 9 Hz, Ar$\underline{H}$), 7.59 (t, 1H, J = 9 Hz, Ar$\underline{H}$), 7.96 (d, 1H, J = 9 Hz, Ar$\underline{H}$); mass spectrum, *m/z* 396 (M^+).

9-Acetyl-4,5,12-trimethoxy-7,8,9,10-tetrahydronaphthacene-6,11-dione (133). A mixture of **132** (2.65 g, 6.7 mmol), selenium dioxide (1.49 g, 13.4 mmol), trifluoroacetic acid (4 mL) and water (2 mL) in methylene chloride (250 mL) was stirred at room temperature for 3 hr. The suspension was decanted and the residue was washed with methylene chloride. Addition of an aqueous calcium oxide solution (200 mL) to the combined organic layer precipitated colloidal selenium, which formed an emulsion. The selenium was removed by filtration through a Celite pad and the organic layer was separated, washed with water (200 mL) and brine, then dried ($MgSO_4$), filtered and evaporated at reduced pressure. Chromatography of the residue on silica gel (100 g, 0-15% EtOAc-CH_2Cl_2) gave 1.98 g (75%) of **133** as orange crystals with mp 183-185 °C after recrystallization (CH_2Cl_2-CCl_4). ^{1}H-NMR ($CDCl_3$) δ 2.2-2.6 (m, 7H, 3-C$\underline{H}_2$, 1-C$\underline{H}$), 2.27 (s, 3H, CO$\underline{CH}_3$), 3.96 (s, 3H, O$\underline{CH}_3$), 4.01 (s, 6H, O$\underline{CH}_3$), 7.06 (d, 1H, J = 9 Hz, Ar$\underline{H}$), 7.60 (t, 1H, J = 9 Hz, Ar$\underline{H}$), 7.94 (d, 1H, J = 9 Hz, Ar$\underline{H}$); mass spectrum, *m/z* 394 (M^+).

Anal. Calcd. for $C_{23}H_{22}O_6$: C, 70.03; H, 5.62. Found: C, 69.90; H, 5.60.

9-Acetyl-6,11-dihydroxy-4-methoxy-7,8,9,10-tetrahydronaphthacene-5,12-dione (56). Boron trichloride (60 mL,

1M soln in CH_2Cl_2, 60 mmol) was added to a solution of **133** (1.83 g, 4.6 mmol) in dry methylene chloride (250 mL) at -60 °C under a nitrogen atmosphere and the mixture was magnetically stirred for 3 hr. Methanol (20 mL) was added to destroy the excess boron trichloride and the dark mixture was allowed to warm to room temperature. Aqueous NaOH (2 N, 130 mL) was added and the resultant blue solution was stirred for 1 hr. Acidification with hydrochloric acid (12 M, 10-20 mL) gave a deep red-colored methylene chloride solution and a red precipitate which was neither soluble in methylene chloride nor water and was presumed to be the boron complex of **56**.

In order to hydrolyze the complex, the methylene chloride solution and the precipitate were combined and the solvent evaporated at reduced pressure. The residue was taken up in methanol (200 mL) containing NaOH (10 mL, 6N) and stirred for 2 hr, then acidified with hydrochloric acid (12M). The resulting mixture was neutralized with aqueous bicarbonate, concentrated, and the residue repeatedly extracted with ethyl acetate (3 x 100 mL). The combined ethyl acetate extracts were evaporated. The dark red residue was dissolved in methylene chloride (200 mL) and eluted through silica gel (20 g). The solvent was evaporated and the residue was recrystallized (CH_2Cl_2-hexanes) to give 1.35 g (79%) of **56** as red crystals with mp 244-247 °C. The TLC behavior and the ^{1}H-NMR spectrum of **56** were identical with an alternatively prepared sample and a mixed mp was undepressed. ^{1}H-NMR ($CDCl_3$) δ 2.29 (s, 3H, $COC\underline{H}_3$), 2.4-3.2 (m, 7H, 3-$C\underline{H}_2$, 1-$C\underline{H}$), 4.08 (s, 3H, $OC\underline{H}_3$), 7.34 (d, 1H, J = 8 Hz, Ar$\underline{H}$), 7.74 (t, 1H, J = 8 Hz, Ar$\underline{H}$), 8.04 (d, 1H, J = 8 Hz, Ar$\underline{H}$); mass spectrum, *m/z* 366 (M^+)

II. Pillaromycinone

4-(2-Hydroxyethyl)benzonitrile (226).

p-(2-Hydroxyethyl)aniline (50 g, 0.36 mol) was dissolved in a solution of sulfuric acid (60 mL, concentrated) and water (60 mL) with mechanical stirring. Additional water (600 mL) was added and the solution was chilled (0-5 °C). A 30% solution of sodium nitrite (92 mL) was added and the solution was stirred for 15 min, then neutralized with aqueous sodium hydroxide (140 mL, 10N). The solution of diazonium salt was slowly poured into a mechanical stirred chilled (0-5 °C) solution of copper(I) cyanide (52 g, 0.58 mol), and sodium cyanide (34 g, 0.70 mol) in water (500 mL) and benzene (200 mL). The reaction mixture was then allowed to warm to room temperature with stirring over a 3 hr. period followed by brief heating to 50° C. After standing for 2 days, a black spongy mass separated from the mixture. The aqueous and benzene layers were separated and the aqueous layer and spongy solid were extracted with benzene (2 x 250 mL). The organic solution was washed successively with 10% hydrochloric acid (2 x 200 mL), water (2 x 200 mL), aqueous bicarbonate (100 mL) and brine (75 mL), then dried ($MgSO_4$), filtered and evaporated at reduced pressure to yield 17.4 g (33%) of **226** a dark yellow oil. The ^{1}H-NMR spectrum showed that the product was pure. ^{1}H-NMR ($CDCl_3$) δ 2.31 (s, 1H, ROH), 2.90 (t, 2H, J = 6.5 Hz, $ArCH_2$-), 3.85 (t, 2H, 6.5 Hz, CH_2OH), 7.2-7.7 (m, 4H, ArH); mass spectrum *m/z* 147 (M^+), 116.

4-(2-Hydroxyethyl)benzoic acid (227). Hydrogen peroxide (40 mL, 30%) was added slowly to a warm (50-60 °C) solution of the nitrile **226** (16.8 g, 0.11 mol) dissolved in 30% potassium hydroxide (350 mL) and ethanol (150 mL). The mixture was heated at reflux for 24 hr, then concentrated to 4/5 volume under reduced pressure. Ice (200 g) was added and the mixture extracted with ether (3 x 200 mL). The combined ether solutions were washed with 2N NaOH (2 x 140 mL). The alkaline aqueous layer was carefully acidified with concentrated sulfuric acid (90 mL) to pH 3-4. The aqueous layer was decanted from the precipitated sodium sulfate salt and extracted with ether (3 x 300 mL). The sulfate salt was also extracted with ether (2 x 150 mL) and the combined organic layers were concentrated to 1/2 volume and washed with water (2 x 150 mL) and brine (50 mL), then dried ($MgSO_4$), filtered, and concentrated to a volume of 250 mL. Addition of carbon tetrachloride (100 mL) and methylene chloride (100 mL) induced crystallization. Recrystallization yielded 10.5 g (55%) of **227** as white crystals, which were pure by NMR. ^{1}H-NMR ($CDCl_3$) δ 3.0 (t, 2H, J = 6.3 Hz, Ar$\underline{CH_2}$-), 3.9 (t, 2H, J = 6.3 Hz, $\underline{CH_2}OH$), 7.2 (d, 2H, Ar$\underline{H}$), 8.0 (d, 2H, Ar$\underline{H}$); mass spectrum, *m/z* 166 (M^+), 136 (M^+-CH_2O), 118.

4-(2-Hydroxyethyl)-2,5-cylohexadienecarboxylic acid (228). The aromatic acid **227** (100 mg, 0.60 mmol) dissolved in dry ethanol (4 mL, distilled over magnesium) was cooled to -70 °C. Ammonia (15-20 mL) was then condensed into the reaction flask with the aid of a

dry ice condenser. With vigorous magnetic stirring, pieces of lithium metal (25 mg) were added, initially generating a blue color which faded in 4-5 min. Excess solid ammonium chloride was added and the reaction was allowed to warm to room temperature. Water (20 mL) was added, and the aqueous layer extracted with hexanes. The aqueous layer was acidified with hydrochloric acid (1-3 mL, 12M) to pH 2-3, then extracted with ether (3 x 20 mL). The ether solution was washed with water (20 mL) and brine (10 mL), then dried ($MgSO_4$), filtered, and concentrated to yield 87 mg (86%) of **228** as clear oil which was shown to be a 1:1 mixture of diastereoisomers by ^{13}C-NMR. ^{1}H-NMR ($CDCl_3$) δ 1.6-1.9 (m, 2H, $C\underline{H}_2$); 2.8-3.0 (m, 1H, Allylic $\underline{H}$); 3.70 (m, 3H, $C\underline{H}_2OH+C\underline{H}CO_2H$); 5.85 (s, 4H, vinyl $\underline{H}$); 7.48 (s, 2H, $CO_2\underline{H}+RO\underline{H}$); ^{13}C-NMR ($CDCl_3$) δ (32.1, 32.7), (37.1, 37.7), (41.7, 42.2), 59.9, 121.8, (130.7, 131.2), 176.9 ($\underline{C}O_2H$).

3-Bromo-2-hydroxy-4-(2-hydroxyethyl)-5-cyclohexenecarboxylic acid β-lactone (231). A solution of bromine (76 μL, 1.47 mmol) in methylene chloride (6 mL) was added to a vigorously stirred solution of the acid **228** (248 mg, 1.47 mmol) dissolved in aqueous bicarbonate (10%, 15 mL). After a few min, the mixture decolorized and after an additional 10 min, the solution was extracted with ether (3 x 30 mL). The ether extract was dried ($MgSO_4$), filtered, and evaporated. Chromatography of the residue on silica gel (20 g, 10-20% EtOAc-CH_2Cl_2) yielded 110 mg of **231** (30%) as an oil. ^{1}H-NMR ($CDCl_3$) δ 1.7-2.0 (m, 2H, $C\underline{H}_2$); 2.5-3.1 (m, 1H, allylic $\underline{H}$); 3.84 (t, 2 H, J = 7 Hz, $C\underline{H}OH$) 4.2-4.4 (m, 1H, -$C\underline{H}$); 4.5-4.7 (m, 1H, -$C\underline{H}$); 4.9-5.1 (m, 1H, -$C\underline{H}$); 5.8-6.2 (m, 2H,

vinyl H). ^{13}C-NMR of the acetate of one isomer, ($CDCl_3$) δ 20.9, 31.7, 32.4, 48.5, 49.4, 61.2, 70.4, 118.4, 132.6; IR (film) cm^{-1} 1820 (β lactone); mass spectrum, *m/z* 248, 246 (M^+, 1), 121 (10), 105 (100).

3-(4-Methylbenzoyl)propenoioc acid (242). A mixture of maleic anhydride (5.7 g, 58.2 mmol), toluene (18.5 mL, 174 mmol), and aluminum chloride (17.0 g, 128 mmol) in nitrobenzene (75 mL) and chloroform (50 mL) was stirred at room temperature for 22 hr. The reaction mixture was poured into ice water (75 mL) and acidified with concentrated hydrochloric acid to pH 1-2. The layers were separated and the organic layer washed with water (75 mL), then extracted with aqueous sodium carbonate (2 x 100 mL, 10%). The bicarbonate solution was acidified with concentrated hydrochloric acid, then extracted with ether (3 x 75 mL). The combined ether extracts were washed with water, then dried ($MgSO_4$), filtered, and evaporated at reduced pressure to give 4.5 g (41%) of **242** of oil. Analysis of the TLC and the ^{1}H-NMR spectrum showed only trace impurities. ^{1}H-NMR ($CDCl_3$) δ 2.44 (s, 3H, ArCH_3), 6.86 (d, 1H, J = 15.6 Hz, vinyl H), 7.34 (d, 2H, J = 8.4 Hz, ArH), 7.92 (d, 2H, J = 8.4 Hz, ArH), 8.00 (d, 1H, J = 10.5 Hz, vinyl H); mass sprectrum, *m/z* 190 (M^+), 173 (M^+-OH), 172, 119 (M^+-CH=CH-CO_2H).

Methyl 3-(4-methylbenzoyl)-3-methoxypropanoate (243). To the acid **242** (1.0 g, 5.2 mmol) in methanol (30 mL) was added sulfuric acid (5 drops, 12N) and the solution was stirred and heated at reflux for 4 hours. Solid sodium bicarbonate (1 g) was added and the

solution was evaporated at reduced pressure. The residue was dissolved in ether (30 mL) and the ether solution was washed with aqueous bicarbonate (15 mL), then dried ($MgSO_4$), filtered, and evaporated to yield 1.1g (100%) of **243** as a light yellow oil. ^{1}H-NMR ($CDCl_3$) δ 2.41 (s, 3H, ArCH_3), 3.47 (s, 3H, OCH_3), 3.3-3.6 (m, 2H, CH_2), 3.79 (s, 3H, CO_2CH_3), 4.5 (dd, 1H, J = 8 Hz, J = 5 Hz, CH_2CHOMe), 7.3-7.5 (m, 2H, ArH), 7.9-8.1 (m, 2H, ArH); mass spectrum, *m/z* 236 (M^+), 204 (M^+ - MeOH), 173, 146, 119, 91.

Methyl 4-hydroxy-4-(4-methylphenyl)-2-butenoate (245). To the keto acid **242**, (675 mg, 3.55 mmol) in aqueous sodium hydroxide (25 mL, 1N) was added sodium borohydride (140 mg, 3.55 mmol) and the mixture stirred at room temperature for 4 hours. The solution was acidified to pH 3 with aqueous concentrated hydrochloric acid, then extracted with ether (2 x 35 mL). The combined ether solution was washed with water (35 mL), then dried ($MgSO_4$), filtered and evaporated at reduced pressure to yield 594 mg of **245** as an oil. ^{1}H-NMR ($CDCl_3$) δ 2.33 (s, 3H, ArCH_3), 5.31 (dd, 1H, J = 5 Hz, J = 1.5 Hz, ArCHOH), 6.12 (dd, 1H, J = 1.5 Hz, J = 15.6 Hz, α vinyl H), 7.0-7.4 (m, 7H, ArH+ vinyl H+CO_2H+ROH). IR (film) cm^{-1} 3200-2800 (CO_2-H), 1699 (C=O) 1654 (C=C) 1600, 1560, 1514, 1469 (Ar C=C).

5-(4-methylphenyl)-2(5H)-furanone (246). To the hydroxy acid **245** (25 mg) in methylene chloride (10 mL) was added methanesulfonyl chloride (2 drop) and collidine (2 drop) and the mixture was stirred for 3 hr at room temperature. The solution was washed with

water (10 mL), then dried ($MgSO_4$), filtered, and evaporated at reduced pressure to give an oil. ^{1}H-NMR ($CDCl_3$) δ 2.3 (s, 3H, ArC<u>H</u>$_3$), 5.38 (dd, 1H, J = 5 Hz, J = 2Hz, Ar-C<u>H</u>(OR)), 6.24 (dd, 1H, J = 15 Hz, J = 2 Hz, vinyl <u>H</u>), 7.0-7.4 (m, 5H, Ar<u>H</u>+vinyl <u>H</u>); IR (film) cm^{-1} 1787 (C=O lactone).

3-(4-Methylbenzoyl)propanoic acid (248). A solution of succinic anhydride (5.0 g, 0.050 mol) and aluminum chloride (14.6 g, 0.110 mol) in nitrobenzene (100 mL) and toluene (5.3 mL, 0.050 mol) was stirred at room temperature for 16 hours. The reaction mixture was poured into a mixture of ice (100 g) and hydrochloric acid (10 mL, 12N) and stirred until the ice melted. The layers were separated and the organic phase was extracted with 1N sodium hydroxide (2 x 25 mL). The aqueous layer was extracted with ether (75 mL), then acidified with concentrated hydrochloric acid (10 mL). Filtration of the product gave 5.65 g (59%) of **248**. The aqueous layer was further extracted with ethyl acetate (100 mL), then dried ($MgSO_4$), filtered, and evaporated at reduced pressure to yield an additional 0.71 g (7%, 66% overall) of **248**. ^{1}H-NMR ($CDCl_3$) δ 2.41 (s, 3H, ArC<u>H</u>$_3$), 2.80 (t, 2H, J = 6.2 Hz, C<u>H</u>$_2$), 3.29 (t, 2H, J = 6.2 Hz, C<u>H</u>$_2$), 7.2-7.4 (m, 2H, Ar<u>H</u>), 7.8-8.0 (m, 2H, Ar<u>H</u>); IR (film) cm^{-1} 3520 (monomeric CO_2-H), 3400-2500 (dimeric CO_2-H), 1750 (dimeric acid C=O), 1714 (monomeric acid C=O), 1685 (ketone C=O).

Ethyl 3-bromo-3-(4-methylbenzoyl)propanoate (249b). A magnetically stirred mixture of the keto acid **248** (145 mg, 0.76 mmol) and cupric bromide (674 mg, 3.0 mmol) in chloroform (2 mL) and

ethyl acetate (2 mL) was heated at reflux for 36 hours. The copper salts were filtered off and the filtrate was washed with water and brine, then dried ($MgSO_4$), filtered, and evaporated. Analysis of a TLC showed two products were present and the ^{1}H-NMR spectrum of the residue indicated the mixture was the bromo keto acid **249a** and bromo keto ethyl ester **249b**.

The above product was dissolved in ethanol (10 mL) containing sulfuric acid (4 drops) and refluxed for 2.5 hours. Solid sodium bicarbonate (0.5 g) was added and the solution was evaporated to dryness. The residue was dissolved in ether (20 mL) and washed with water (10 mL), then dried ($MgSO_4$), filtered, and evaporated to give 175 mg (77%) of **249b**. ^{1}H-NMR ($CDCl_3$) δ 1.23 (t, 3H, J = 7.1 Hz, $OCH_2C\underline{H}_3$), 2.43 (s, 3H, $ArC\underline{H}_3$), 3.10 (dd, 1H, J = 6.2 Hz, J = 17.1 Hz, $C\underline{H}_2$), 3.52 (dd, 1H, J = 8.4 Hz, J = 17.1 Hz, $C\underline{H}_2$), 4.14 (q, 2H, J = 7.1 Hz, $OC\underline{H}_2CH_3$), 5.49 (dd, 1H, J = 6.2 Hz, J = 8.4 Hz, $C\underline{H}Br$), 7.2-7.5 (m, 2H, $Ar\underline{H}$), 7.9-8.1 (m, 2H, $Ar\underline{H}$).

Ethyl 3-bromo-4-hydroxy-4-(4-methylphenyl)-butanoate (250). Sodium borohydride (23 mg, 0.61 mmol) was slowly added to the bromo keto ester **249b** (125 mg, 0.58 mmol) in methanol (15 mL). The reaction was stirred for 0.5 hr. at room temperature and then acetone (2 mL) was added. After 10 min, ether (50 mL) and sodium chloride were added to the reaction and the layers were separated. The ether layer was washed with water, then dried ($MgSO_4$), filtered, and evaporated to yield 140 mg (80%) of **250** as an oil. ^{1}H-NMR ($CDCl_3$) δ 1.25 (t, 3H, J = 7.2 Hz, $OCH_2C\underline{H}_3$), 2.34 (s, 3H, $ArC\underline{H}_3$), 2.5-3.0 (m, 2H, $C\underline{H}_2$), 4.14

(q, 2H, J = 7.2 Hz, $OC\underline{H}_2CH_3$), 4.5-4.9 (m, 2H, -C<u>H</u>(OH)C<u>H</u>Br-), 7.1-7.4 (m, 4H, Ar<u>H</u>); mass spectrum, *m/z* 302, 300 (M^+), 283, 285 (M^+-OH), 257, 255 M^+-OEt), 221, 220, 175, 174, 148.

4-Bromo-5-(4-methylphenyl)-3,4-dihydro-2(5H)-furanone (251). The bromohydroxy ester **250** (130 mg, 0.43 mmol) and *p*-toluenesulfonic acid (0.5 mg) were stirred and heated at reflux in benzene (65 mL) for 20 hours. The solution was washed with aqueous sodium bicarbonate (20 mL) and water (10 mL), then dried ($MgSO_4$), filtered, and evaporated to give **251**. ^{1}H-NMR δ 2.4 (s, 3H, $ArC\underline{H}_3$), 3.14 (dd, 1H, J = 20 Hz, J = 2 Hz, $C\underline{H}_2$), 3.42 (dd, 1H, J = 20 Hz, J = 6 Hz, $C\underline{H}_2$), 4.84 (ddd, 1H, J = 6 Hz, J = 4 Hz, J = 2 Hz, C<u>H</u>Br), 5.56 (d, 1H, J = 4 Hz, ArC<u>H</u>(OR)), IR (film) cm^{-1} 1792 (lactone C=O).

2-(2-Cyclopentenyl)ethanol (253). 2-Cyclopentene acetic acid (**252**) (14.7 g, 0.117 mol) was added dropwise to a magnetically stirred suspension of lithium aluminum hydride (4.50 g, 0.118 mol) in anhydrous ether (250 mL) at room temperature under nitrogen. The reaction was stirred for an additional hour, then quenched by sequential slow addition of water (4.5 mL), 15% aqueous sodium hydroxide (4.5 mL), and water (13.5 mL). The reaction was filtered and the ether was evaporated to furnish 12.08 g (92%) of **253** as an odorous liquid. ^{1}H-NMR ($CDCl_3$) δ 1.2-1.8 (m, 3H, 3 methylene <u>H</u>), 1.8-2.5 (m, 3H, 2 allylic $C\underline{H}_2$, 1 methylene <u>H</u>), 2.5-2.9 (m, 1H, allylic methine), 3.03 (s, 1H, RO<u>H</u>), 3.65 (t, 2H, J = 6.9 Hz, -$C\underline{H}_2$OH), 5.70 (brd s, 2H, vinyl <u>H</u>); ^{13}C-NMR ($CDCl_3$) δ 29.7, 31.7, 38.7, 42.1, 61.3,

130.3, 134.5 (C=C); IR (film) cm^{-1} 3600-3100 (O-H), 3052 (vinyl C-H), 2931 (aliphatic C-H), 2852; mass spectrum, *m/z* 112 (M^+), 94 (M^+-H_2O), 81 (M^+-CH_2OH), 79, 67, 66.

2-Cyclopentenylethanal (254). A solution of dimethyl sulfoxide (7.60 mL, 107 mmol) in methylene chloride (5 mL) was added dropwise to a chilled (-60 °C) solution of oxalyl chloride (4.70 mL, 53.8 mmol) in methylene chloride (100 mL, anhydrous) and the solution stirred for 15 min. A solution of alcohol **253** (3.01 g, 26.9 mmol) in methylene chloride (8 mL) was added dropwise to the reaction (-60° C) and the reaction continued for 30 min. Triethylamine (22 mL) was added in a thin stream resulting in the formation of a precipitate. The reaction mixture was stirred for 15 min. at -60 °C, then warmed to room temperature and stirred for an additional 20 min. Water (20 mL) was added and the layers were separated. The organic phase was washed with HCl (100 mL, 1N), water (2 x 75 mL), aqueous sodium bicarbonate (75 mL), and brine (50 mL), then dried ($MgSO_4$), filtered, and evaporated at reduced pressure to yield 2.84 g (96%) of **254** as a highly odorous oil. ^{1}H-NMR ($CDCl_3$) δ 1.0-1.9 (m, 2H, -C<u>H</u>$_2$), 2.0-2.8 (m, 4H, allylic-C<u>H</u>$_2$, C<u>H</u>$_2$CHO), 2.9-3.4 (m, 1H, allylic-CH), 5.6-5.9 (m, 2H, vinyl <u>H</u>), 9.78 (t, 1H, J = 3 Hz, Aldehyde C<u>H</u>O).

Methyl 4-(2-cyclopentenyl)-3-butenoate (255). Trimethylphosponoacetate (18.4 mL, 0.114 mole) was added dropwise at room temperature to an oil free suspension of sodium hydride (5.3 g, 50%,

0.109 mol) in THF (250 mL, anhyd). The formation of solids required occasional shaking by hand to ensure thorough mixing. After 2.5 hours, the aldehyde **254** (10.0 g, 0.091 mol) was added dropwise and the solids dissolved. The mixture was stirred for an additional hour, then water (10 mL) added slowly. The solution was evaporated under reduced pressure and the residue dissolved in ether (150 mL). The ether solution was washed with dilute hydrochloric acid (75 mL), aqueous sodium bicarbonate (75 mL) and brine (50 mL), then dried, ($MgSO_4$), filtered, and evaporated to yield 14.4 g of a dark liquid, which on distillation (98-104 °C / 9 mm) afforded 10.3 g (64%) of **255** as a pale yellow oil. ^{1}H-NMR ($CDCl_3$) δ 1.2-1.8 (m, 1H, -C<u>H</u>$_2$), 1.8-2.5 (m, 5H, 2 allylic-C<u>H</u>$_2$, 1 methylene <u>H</u>), 2.5-3.0 (m, 1H, allylic-C<u>H</u>), 3.72 (s, 3H, $CO_2C\underline{H}_3$), 5.6-6.0 (m, 3H, vinyl <u>H</u>), 6.96 (dt, 1H, J = 15.4 Hz, J = 7.5 Hz, β vinyl <u>H</u>).

Ethyl 2-methoxy-6-phenylthiomethylbenzoate (257). A solution of ethyl 2-methoxy-6-methyltoluate (**256**, 15.3 g, 78.9 mmol) in THF (30 mL, anh.) was added slowly to a chilled (-70 °C) solution of LDA prepared from *n*-BuLi (80.4 mmol) and diisopropylamine (82.0 mmol) in tetrahydrofuran (180 mL). The resultant red anion solution was added dropwise (*via* a dry ice jacketed addition funnel) to a chilled (-70 °C) solution of diphenyl disulfide (18.9 g, 86.8 mmol) in THF (200 mL). The reaction was stirred for 20 min, then an ammonium chloride (4.5 g in 50 mL water) solution was added and the reaction was warmed to room temperature. The solution was concentrated to 1/3 volume then diluted with ether (400 mL). The layers were separated and the organic phase was

washed successively with 2N aqueous sodium hydroxide (3 x 100 mL), 1N HCl (100 mL), aqueous sodium bicarbonate (50 mL), and brine, then dried ($MgSO_4$), filtered, and evaporated to yield 26.4 g of **257** as an oil which according to TLC analysis was contaminated with diphenyl disulfide. ^{1}H-NMR ($CDCl_3$) δ 1.36 (t, 3H, J = 7.3 Hz, $OCH_2\underline{CH_3}$), 3.82 (s, 3H, $OC\underline{H_3}$), 4.14 (s, 2H, $ArC\underline{H_2}S$), 4.39 (q, 2H, J = 7.3 Hz, $OC\underline{H_2}CH_3$), 6.7-7.0 (m, 2H, Ar$\underline{H}$), 7.1-7.6 (m, 6H, Ar$\underline{H}$).

Ethyl 2-methoxy-6-phenylsulfoxomethylbenzoate (200). A solution of the crude sulfide **257** (26.4 g) in methanol (800 mL) was added to a solution of sodium periodate (16.9 g) in water (100 mL) and the mixture stirred at room temperature for 60 hr. The solids were filtered and the filtrate concentrated to 1/2 volume. Brine (300 mL) was added and the mixture was extracted with ether (4 x 300 mL). The combined ether solution was washed with brine, then dried ($MgSO_4$), filtered, and evaporated at reduced pressure to yield 26.1 g of an orange oil. Chromatography of the oil on silica gel (50 g, 30-100% CH_2Cl_2 in hexanes) yielded 14.4 g (57% from **256**) of **200** as a viscous oil. ^{1}H-NMR ($CDCl_3$) δ 1.39 (t, 3H, J = 7.2 Hz, $OCH_2\underline{CH_3}$), 3.83 (s, 3H, $OC\underline{H_3}$), 4.00 (d, 1H, J = 14 Hz, $ArC\underline{H_2}S$), 4.12 (d, 1H, J =16 Hz, $ArC\underline{H_2}S$) 4.39 (q, 2H, J = 7.2 Hz, $OC\underline{H_2}CH_3$), 6.61 (d, 1H, J = 7.7 Hz, Ar$\underline{H}$), 6.89 (d, 1H, J = 7.7 Hz, Ar$\underline{H}$), 7.19 (t, 1H, J = 7.7 Hz, Ar$\underline{H}$), 7.47 (br s, 5H, Ar$\underline{H}$); ^{13}C-NMR ($CDCl_3$) δ 13.8 ($\underline{C}H_3$), 55.7, 61.0, 62.0, 111.2, 123.2, 123.6, 123.7, 128.6, 129.1, 130.4, 130.8, 143.1, 156.8, 166.8 ($\underline{C}O_2R$).

Methyl 3-(2-cyclopentenylmethyl)-1-hydroxy-8-methoxynaphthalene-2-carboxylate (258). A solution of the sulfoxide **200** (1.33 g, 4.18 mmol) in THF (13 mL, anhydrous), under nitrogen, was added dropwise to a chilled (-60 °C) solution of LDA prepared from *n*-BuLi (12.5 mmol) and diisopropylamine (12.9 mmol) in THF (15 mL). Copper(I) cyanide (101 mg, 1.12 mmol) was added and the resultant black solution stirred for 5 min. A solution of **255** (914 mg, 5.51 mmol) dissolved in THF (5 mL) was added next. The reaction was stirred for 20 min at -60° C, then warmed to room temperature and stirred for an additional 2 hr. *t*-Butanol (1.8 mL, anhydrous) was added and the reaction was refluxed for 2.5 hr. After the reaction was cooled to room temperature, hydrochloric acid (15 mL, 1N) was added and the mixture was extracted with ether (2 x 25 mL). The combined organic solution was washed with hydrochloric acid (20 mL, 1N), aqueous sodium bicarbonate, brine, then dried ($MgSO_4$), filtered, and evaporated to yield 1.60 g of a dark oil. Chromatography of the oil on silica gel (200 g, 15-30% EtOAc in hexanes) yielded 589 mg (45%) of **258** as a pale yellow oil which solidified under vacuum. ^{1}H-NMR ($CDCl_3$) δ 1.2-1.8 (m, 1H, -C$\underline{H}_2$), 1.8-2.5 (m, 3H, allylic-C$\underline{H}_2$, 1 methylene $\underline{H}$), 2.6-3.2 (m, 3H, allylic-CH, benzylic-C$\underline{H}_2$), 3.95 (s, 3H, OC$\underline{H}_3$), 3.99 (s, 3H, OC$\underline{H}_3$), 5.6-5.8 (m, 2H, vinyl $\underline{H}$), 6.71 (t, 1H, J = 4 Hz, Ar$\underline{H}$), 7.11 (s, 1H, Ar$\underline{H}$), 7.30 (d, 2H, J = 4 Hz, Ar$\underline{H}$), 9.91 (s, 1H, ArO$\underline{H}$); IR (film) cm^{-1} 3400 (O-H), 3060 (vinyl C-H), 2949 (aliphatic C-H), 2848 (ArOMe), 1722 (C=O), 1636 (C=C), 1610, 1582, 1500, 1460 (Ar C=C); mass spectrum *m/z* 312 (M^+), 281 (M^+-OMe), 245 (M^+-C_5H_7), 214 (M^+-OMe -C_5H_7), 186.

Methyl 3-(2-cyclopentenylmethyl)-1,8-dimethoxy-2-naphthalenecarboxylate (259). The magnetically stirred mixture of the phenolic ester **258** (190 mg, 0.61 mmol), potassium carbonate (77 mg, 5.59 mmol), and dimethyl sulfate (290 mL, 3.0 mmol) in dry methyl ethyl ketone (15 mL) was heated at reflux for 16 hr. The solution was cooled, and the solids filtered. Triethylamine (0.5 mL) was added to the filtrate and the mixture stirred for 1 hr at room temperature. The solution was concentrated and the residue dissolved in ether (40 mL). The ether solution was washed with hydro-chloric acid (1N,15 mL), aqueous sodium bicarbonate (15 mL), and brine (10 mL), then dried ($MgSO_4$), filtered, and concentrated under reduced pressure to yield 213 mg of **259** as an oil. The product was used in the next step without purification. ^{1}H-NMR ($CDCl_3$) δ 1.2-2.4 (m, 4H, allylic-C$\underline{H}_2$, -C$\underline{H}_2$), 2.6-2.8 (m, 2H, allylic-C$\underline{H}$, 1 benzylic $\underline{H}$), 2.8-3.2 (m, 1H, 1 benzylic $\underline{H}$), 3.87 (s, 3H, OC$\underline{H}_3$), 3.93 (s, 3H, OC$\underline{H}_3$), 3.96 (s, 3H, OC$\underline{H}_3$), 5.6-5.8 (m, 2H, vinyl $\underline{H}$), 6.78 (t, 1H, J = 7 Hz, Ar$\underline{H}$), 7.2-7.3 (m, 3H, Ar$\underline{H}$); IR (film) cm^{-1} 3054 (vinyl C-H), 3003, 2940 (aliphatic C-H), 2840 (ArOMe), 1730 (C=O), 1624 (C=C), 1600, 1570, 1500, 1460 (Ar C=C).

3-(2-Cyclopentenylmethyl)-2-hydroxymethyl-1,8-dimethoxynaphthalene (260). A solution of the ester **259** (150 mg, 0.46 mmol) in anhydrous ether (5 mL) was added dropwise to a magnetically stirred suspension of lithium aluminum hydride (18 mg) in ether (15 mL) at room temperature. The mixture was stirred for 30 min,

then water (18 ml), 15% sodium hydroxide (18 ml), and water (36 ml) were added successively. The mixture was filtered through magnesium sulfate and the filtrate evaporated to yield 150 mg of **260** as an oil. The product was used in the next step without purification. ^{1}H-NMR ($CDCl_3$) δ 1.4-1.8 (m, 1H, -C$\underline{H}_2$), 1.8-2.6 (m, 4H, 1 methylene $\underline{H}$, allylic-C$\underline{H}_2$, RO$\underline{H}$), 2.7-3.1 (m, 3H, benzylic C$\underline{H}_2$, allylic-C$\underline{H}$), 3.90 (s, 3H, OC$\underline{H}_3$), 4.00 (s, 3H, OC$\underline{H}_3$), 4.88 (s, 2H, ArC$\underline{H}_2$OH), 5.6-5.8 (m, 2H, vinyl $\underline{H}$), 6.80 (t, 1H, J = 4 Hz, Ar$\underline{H}$), 7.34 (t, 3H, J = 4 Hz, Ar$\underline{H}$), 7.40 (s, 1H, Ar$\underline{H}$); IR (film) cm^{-1} 3400 (ROH), 3052 (vinyl C-H), 2934 (aliphatic C-H), 2847 (ArOMe), 1624 (C=C), 1600, 1570, 1460 (Ar C=C).

3-(2-Cyclopentenylmethyl)-1,8-dimethoxy-2-napthalenecarboxaldehyde (261). The alcohol **260** (108 mg, 0.36 mmol) dissolved in methylene chloride (5 mL) was added to a solution of CrO_3 (223 mg, 2.23 mmol) and pyridine (360 mL, 4.46 mmol) in methylene chloride (15 mL) and stirred for 15 min at room temperature. Ether (30 mL) was added and the mixture filtered. The solution was washed successively with sodium hydroxide (10 mL, 1N), HCl (10 mL, 1N), aqueous sodium bicarbonate (10 mL), and brine (10 mL), then dried ($MgSO_4$), filtered, and evaporated at reduced pressure. Chromatography of the residue on silica gel (5 g, CH_2Cl_2) yielded 87 mg (94% from **258**) of **261** as an oil. ^{1}H-NMR ($CDCl_3$) δ 1.4-2.4 (m, 4H, allylic-C$\underline{H}_2$, -C$\underline{H}_2$), 2.9-3.2 (m, 3H, allylic-C$\underline{H}$, benzylic-C$\underline{H}_2$), 3.95 (s, 3H, OC$\underline{H}_3$), 4.04 (s, 3H, OC$\underline{H}_3$), 5.6-5.8 (m, 2H, vinyl $\underline{H}$), 6.86 (dd, 1H, J = 8 Hz, J = 2 Hz, Ar$\underline{H}$), 7.2-7.6 (m, 3H, Ar$\underline{H}$), 10.73 (s, 1H, Aldehyde C$\underline{H}$O); IR (film) cm^{-1} 3050 (vinyl C-H), 2927

(aliphatic C-H), 2849 (ArOMe), 1681 (C=O), 1621 (C=C), 1600, 1566, 1492, 1460, (Ar C=C); mass spectrum, *m/z* 296 (M^+), 230, 229 (M^+-C_5H_7).

Diethyl 3-oxocyclopentylmalonate (271). Diethylmalonate (**269**, 46 mL, 305 mmol) was added to a chilled (0 °C) magnetically stirred solution of sodium ethoxide prepared from sodium (220 mg) and anhydrous ethanol (150 mL). 2-Cyclopentenone (**270**, 25.6 g, 312 mmol) was added and after the reaction solution had stirred for 4.5 hours at 0 °C, it was slowly warmed to room temperature. Acetic acid (0.7 mL) was added and the ethanol evaporated at reduced pressure. The residue was dissolved in ether (300 mL) and washed successively with water (100 mL), aqueous sodium bicarbonate (100 mL) and brine (50 mL), then dried ($MgSO_4$), filtered, and concentrated to yield 66.6 g (90%) of **271** as a pale yellow oil which was shown to be pure by NMR and analysis of a TLC. ^{1}H-NMR ($CDCl_3$) δ 1.27 (t, 6H, J = 7.0 Hz, $OCH_2C\underline{H}_3$), 1.5-3.1 (m, 7H, ring -$C\underline{H}_2$ & -C<u>H</u>), 3.32 (d, 1H, J = 10 Hz, C<u>H</u>(CO_2R)), 4.20 (q, 2H, J = 7.0 Hz, $OC\underline{H}_2CH_3$), 4.22 (q, 2H, J = 7.0 Hz, $OC\underline{H}_2CH_3$).

3-Oxocyclopentylacetic acid (272a). The diester **271** (19.9 g, 77 mmol) was dissolved in acetic acid (120 mL) and concentrated sulfuric acid (7.3 mL) added. The reaction was heated at reflux for 24 hr. Approximately half of the acetic acid was then removed by distillation. The solution was cooled to room temperature, and sodium acetate (20 g) was added. The mixture was stirred for 15 min and the precipitated salts removed by filtration. The filtrate was concentrated and the residue was

dissolved in sodium hydroxide (1N, 100 mL) and extracted with ether (100 mL). The aqueous layer was acidified with concentrated hydrochloric acid and extracted with ethyl acetate (3 x 100 mL). The combined ethyl acetate solution was dried ($MgSO_4$), filtered, and concentrated to yield 10.7 g (98%) of **272a** as a dark oil, which was used in the next step without further purification. ^{1}H-NMR ($CDCl_3$) δ 1.2-3.0 (m, 9H, ring and chain -C<u>H</u>$_2$ & -C<u>H</u>), 10.0 (brd s, 1H, CO_2<u>H</u>); ^{13}C-NMR ($CDCl_3$) δ 28.6, 32.7, 37.8, 38.8, 44.0, 176.6 (acid <u>C</u>=O), 219.3 (ketone <u>C</u>=O); IR (film) cm^{-1} 3500-2500 (CO_2-H), 2965 (aliphatic C-H), 1734 (C=O); mass spectrum, *m/z* 142 (M^+, 18), 113 (11), 83 (100).

Methyl 3-oxocyclopentylacetate (272b). The keto acid **272a** (20.3 g, 143 mmol), water (20 mL), and concentrated sulfuric acid (4 mL) were dissolved in methanol (500 mL) and heated under reflux for 16 hr. The reaction was cooled to room temperature and sodium bicarbonate (12 g) added. The methanol was evaporated and the residue dissolved in ether (500 mL). The ether solution was washed successively with water (100 mL), aqueous bicarbonate (2 x 100 mL), water (100 mL), and brine (50 mL). The combined aqueous layers were again extracted with ether (3 x 100 mL) and the combined ether layers were washed with aqueous bicarbonate (70 mL) and brine (50 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated to give 20 g (90%) of **272b** as a pale yellow oil. ^{1}H-NMR showed about 10% contamination by the ketal lactone **273** as evidenced by: δ 3.18 (s, 3H, OC<u>H</u>$_3$). ^{1}H-NMR ($CDCl_3$) δ 1.4-2.8 (m, 9H, ring and chain -C<u>H</u>$_2$ & -C<u>H</u>), 3.69 (s, 3H, OC<u>H</u>$_3$); IR (film) cm^{-1}

2956, 2910 (aliphatic C-H), 1745 (ketone C=O), 1734 (ester C=O); ^{13}C-NMR ($CDCl_3$) δ 28.8, 33.1, 37.8, 39.0, 44.2, 51.2, 172.0 (ester C=O), 217.4 (ketone C=O); mass spectrum *m/z* 156 (M^+, 21), 125 (M^+-MeO, 28), 99 (49).

Methyl 3,3-(ethane-1',2'-diyldioxy)cyclopentyl-acetate (274). A magnetically stirred solution of the keto ester **272b** (20.0 g, 128 mmol), ethylene glycol (10 mL, 177 mmol), and pyridinium *p*-toluenesulfonate in benzene (500 mL) was heated at reflux for 24 hr. The benzene was evaporated at reduced pressure and the residue dissolved in ether (500 mL). The ether solution was washed with aqueous sodium bicarbonate (2 x 100 mL) and brine (100 mL), then dried ($MgSO_4$), filtered, and concentrated to yield 24.2 g (95%) of **274** as an oil, which was shown to be pure by NMR. ^{1}H-NMR ($CDCl_3$) δ 1.2-2.5 (m, 9H, ring and chain -C<u>H</u>$_2$ & -C<u>H</u>), 3.66 (s, 3H, OC<u>H</u>$_3$), 3.89 (s, 4H, OC<u>H</u>$_2$C<u>H</u>$_2$O); ^{13}C-NMR ($CDCl_3$) δ 29.6, 33.5, 35.4, 39.4, 41.9, 50.3, 63.7 (O<u>C</u>H$_3$), 63.8 (O<u>C</u>H$_3$), 117.0 (O-C-O), 172.5 (ester <u>C</u>=O); IR (film) cm^{-1} 2954, 2884 (aliphatic C-H), 1738 (ester C=O); mass spectrum *m/z* 200 (M^+, 3), 171 (M^+-C_2H_4-H, 40), 127 (M^+-CH_2CO_2Me, 77), 99 (100).

2-(3,3-(Ethane-1',2'-diyldioxy)-cyclopentyl)-ethanol (275). A solution of the ketal ester **274** (24.2 g, 121 mmol) dissolved in ether (100 mL) was added slowly to a chilled (0 °C) suspension of lithium aluminum hydride (4.5 g, 118 mmol) in anhydrous ether (400 mL). The reaction was stirred for 45 min, then water (4.5 mL), 15% aqueous sodium hydroxide (4.5 mL), and water (13.5 mL) were

successively added. The mixture was filtered through magnesium sulfate and the filtrate evaporated at reduced pressure to yield 19.5 g (94%) of **275** as an oil which was pure by NMR. ^{1}H-NMR ($CDCl_3$) δ 1.1-2.3 (m, 9H, ring and chain -C<u>H</u>$_2$ & -C<u>H</u>), 3.66 (t, 2H, J = 7.0 Hz, C<u>H</u>$_2$OH), 3.89 (s, 4H, OC<u>H</u>$_2$C<u>H</u>$_2$O); IR (film) cm^{-1} 3400 (O-H), 2960, 2932, 2880 (aliphatic C-H); ^{13}C-NMR ($CDCl_3$) δ 29.9, 33.9, 35.5, 38.3, 42.3, 60.6 (O<u>C</u>H$_2$), 63.5 (O<u>C</u>H$_2$), 63.7 (O<u>C</u>H$_2$), 117.4 (O-C-O); mass spectrum, *m/z* 172 (M^+, 2), 143 (M^+-C_2H_4-H, 31), 127 (M^+-CH_2CH_2OH, 31), 113 (19), 99 (100).

3,3-(Ethane-1',2'-diyldioxy)cyclopentylethanal (276). The alcohol **275** (6.2 g, 36 mmol) dissolved in methylene chloride (30 mL) was added in a thin stream to a magnetically stirred chilled (0° C) solution of Collins reagent prepared from pyridine (36 mL, 44 mmol) and CrO_3 (22 g, 0.22 mmol) in dry methylene chloride (300 mL), and the reaction allowed to stand for 1 hour (chromium precipitate formation eventually prevented stirring). The reaction mixture was decanted and the solid residue washed with ether (4 x 100 mL). The organic layers were combined and concentrated to 1/4 volume. Ether (200 mL) was added and the mixture filtered through Celite to remove chromium salts. The organic solution was washed with water (2 x 100 mL) and aqueous sodium bicarbonate (2 x 70 mL), then dried ($MgSO_4$), filtered, and concentrated to yield 5.4 g (88%) of **276** as a pale yellow oil, which by NMR contained a trace of pyridine. Due to the facile migration of the ketal functionality to the aldehyde carbonyl, the product was immediately used in the next step. ^{1}H-NMR ($CDCl_3$) δ 1.1-2.2 (m, 7H, ring -C<u>H</u>$_2$ & -C<u>H</u>), 2.3-2.6 (m, 2H,

-C<u>H</u>$_2$CHO) 3.89 (s, 4H, OC<u>H</u>$_2$C<u>H</u>$_2$O, 9.75 (t, 1H, J = 2 Hz, Aldehyde C<u>H</u>O); IR (film) cm^{-1} 2957, 2883 (aliphatic C-H), 2724 (aldehyde C-H), 1723 (aldehyde C=O); ^{13}C-NMR ($CDCl_3$) δ 29.1, 30.6, 34.8, 35.0, 41.4, 63.2 (O<u>C</u>H$_2$), 116.8 (O-C-O), 200.7 (<u>C</u>=O); mass spectrum, *m/z* 141 (M^+ -C_2H_3, 13), 127 (M^+-CH_2CHO, 88), 113 (42), 99 (100).

Methyl 4-(3,3-(ethane-1',2'-diyldioxy)cyclopentyl)-2-butenoate (277). Trimethylphosphonoacetate (7.8 mL, 48 mmol) was added to an oil free suspension of sodium hydride (2.3 g, 48 mmol) in dry dimethylformamide (250 mL) at 0° C and the mixture stirred for 2 hr. A solution of the aldehyde **276** (5.4 g, 32 mmol) in dimethylformamide (50 mL) was added slowly and the reaction stirred for 4 hours at room temperature. Water (150 mL) and ether (150 mL) were added and the layers separated. The organic layer was washed with water (75 mL), aqueous sodium bicarbonate (75 mL), and brine (50 mL), then dried ($MgSO_4$), filtered, and evaporated at reduced pressure. Chromatography of the residue on silica gel (100 g, 1:1 EtOAc-Hexanes) gave 4.0 g (56%) of **277** as an oil. Analysis of the ^{1}H-NMR showed that the product consisted of a 2:1 mixture of *E/Z* isomers. ^{1}H-NMR ($CDCl_3$) δ 1.2-3.0 (m, 9H, ring and allylic C<u>H</u>$_2$ & C<u>H</u>), 3.70, 3.72 (s, 3H combined, OC<u>H</u>$_3$), 3.89 (s, 4H, OC<u>H</u>$_2$C<u>H</u>$_2$O), 5.80 (brd d, J = 11.9 Hz), and 5.83 (brd d, J = 15.8 Hz), (1H combined (vinyl <u>H</u>), 6.23 (dt, J = 11.9 Hz, J = 7.2 Hz) and 6.93 (dt, J = 15.8 Hz, J = 6.9 Hz), 1H combined (vinyl <u>H</u>); ^{13}C-NMR ($CDCl_3$) δ 29.5, 35.3, 36.1, 37.8, 41.8, (50.4, 50.7 O<u>C</u>H$_3$), 63.6 (O<u>C</u>H$_2$), 63.8 (O<u>C</u>H$_2$), (117.0, 117.2, O-<u>C</u>-O), (119.4, 121.3),

(147.3, 148.3) (Ar<u>C</u>), 166.2 (<u>C</u>=O); mass spectrum, *m/z* 226 (M^+, 56), 195 (M^+-MeO, 24), 167 (M^+-CO_2Me, 18), 153 (34), 127 (100).

Methyl 1-hydroxy-8-methoxy-3-(3,3-(ethane-1',2'-diyldioxycyclopentylmethyl)naphthalene-2-carboxylate (279a). The sulfoxide **200** (1.3 g, 4.1 mmol) was added slowly to a chilled (-60° C), magnetically stirred solution of LDA prepared from *n*-BuLi (12.2 mmol) and diisopropylamine (12.8 mmol) in anhydrous dimethoxyethane (40 mL) under a nitrogen atmosphere. After 4 min, copper(I) cyanide (35 mg, 0.39 mmol) was added to the red colored anion solution, generating a black colored solution, which was stirred an additional 5 min. The Michael acceptor **277** (1.0 mL, 4.4 mmol), dissolved in THF (5 mL), was added to the anion solution and after 15 min the reaction was allowed to warm slowly to room temperature and stirred 5 hr.

Anhydrous *t*-butanol (1.8 mL) was added and the solution heated at reflux for 40 min, then cooled and quenched with water (5 mL). Ether (300 mL) and brine (100 mL) were added and the layers separated. The organic layer was washed with aqueous sodium bicarbonate (2 x 100 mL) and brine (100 mL), then dried ($MgSO_4$), filtered, and concentrated to yield 2.13 g of a dark oil. Chromatography of the oil on silca gel (150 g, 15-30% EtOAc-hexanes) yielded 495 mg (33%) of **279a** as an yellow orange oil. ^{1}H-NMR ($CDCl_3$) δ 1.2-2.6 (m, 7H, cyclopentyl C<u>H</u>$_2$ & C<u>H</u>), 2.79 (d, 1H, J = 7.0 Hz, ArC<u>H</u>$_2$-), 3.87 (s, 4H, OC<u>H</u>$_2$C<u>H</u>$_2$O), 3.96 (s, 3H, OC<u>H</u>$_3$), 4.00 (s, 3H, OC<u>H</u>$_3$), 6.70 (dd, 1H, J = 7 Hz, J = 5 Hz, Ar<u>H</u>), 7.10 (s, 1H, Ar<u>H</u>), 7.29 (d, 1H, J = 7 Hz, Ar<u>H</u>), 7.32 (d, 1H, J = 5 Hz, Ar<u>H</u>), 9.49 (s, 1H, ArO<u>H</u>); ^{13}C-NMR ($CDCl_3$) δ

29.7, 35.3, 38.0, 39.0, 42.0, 51.4, 55.5, 63.4, 63.5, 103.6, 112.5, 115.9, 117.0, 118.4, 120.4, 126.6, 135.9,136.9, 152.3, 155.8, 168.4 ($\underline{C}O_2R$); IR (KBr) cm^{-1} 3370 (O-H), 2950, 2882 (aliphatic C-H), 1727 (C=O), 1635, 1609, 1582, 1500, 1457 (Ar C=C); mass spectrum, *m/z* 372 (M^+, 34), 246 (6), 127 (100), 99 (27).

Methyl 1,8-dimethoxy-3-(3,3-(ethane-1',2'-diyl-dioxy)cyclopentylmethyl)naphthalene-2-carboxylate (279b). A magnetically stirred solution of the naphthalene **279a** (495 mg, 1.33 mmol), anhydrous potassium carbonate (0.90 g, 6.5 mmol), and dimethyl sulfate (190 ml, 1.99 mmol) in methyl ethyl ketone (25 mL) were heated at reflux under a nitrogen atmosphere for 3.5 hr. The reaction was cooled to room temperature and the solids filtered. Triethylamine (0.5 mL) was added to the filtrate and the solution stirred 0.5 hr. The solvent was evaporated at reduced pressure and the residue dissolved in ether (60 mL). The ether solution was washed with aqueous sodium bicarbonate (2 x 25 mL) and brine (25 mL), then dried ($MgSO_4$), filtered, and evaporated to yield 504 mg (98%) of **279b** as an oil, which was shown to be pure by NMR. ^{1}H-NMR ($CDCl_3$) δ 1.0-2.6 (m, 7H, cyclopentyl $C\underline{H}_2$ & $C\underline{H}$), 2.73 (d, 1H, J = 7.0 Hz, $ArC\underline{H}_2$-), 3.87 (s, 7H, $OC\underline{H}_3$+ $OC\underline{H}_2C\underline{H}_2O$ +), 3.94 (s, 3H, $OC\underline{H}_3$), 3.98 (s, 3H, $OC\underline{H}_3$), 6.78 (dd, 1H, J = 7 Hz, J = 5 Hz, Ar$\underline{H}$), 7.3-7.4 (m, 3H, Ar$\underline{H}$); ^{13}C-NMR ($CDCl_3$) δ 30.2, 35.9, 38.2, 39.0, 42.5, 52.0, 55.9, 63.7, 63.9, 64.1, 105.6, 117.6, 118.0, 120.4, 124.1, 127.1, 136.0, 137.2, 153.7, 156.0, 168.8 ($\underline{C}O_2R$); IR (KBr) cm^{-1} 2940, 2880 (aliphatic C-H), 2840 (ArOMe), 1730 (C=O), 1624, 1600, 1571, 1460 (Ar C=C); mass spectrum *m/z* 386 (M^+, 56), 260 (13), 127 (100), 99 (35).

1,8-Dimethoxy-3-(3,3-(ethane-1',2'-diyldioxy)-cyclopentylmethyl)-2-hydroxymethylnaphthalene (280). A solution of the ester **279b** (500 mg, 1.29 mmol) dissolved in ether (10 mL) was added to a chilled (0 °C), magnetically stirred suspension of lithium aluminum hydride (98.0 mg, 2.58 mmol) in anhydrous ether (30 mL) under a nitrogen atmosphere. The reaction was stirred 0.5 hour (25 °C), then water (1.0 mL), 15% aqueous sodium hydroxide (1.0 mL), and water (3.0 mL) were added successively. The mixture was filtered through magnesium sulfate, and the filtrate evaporated to give 535 mg of an oil. Chromatography of the residue on silica gel (20 g, 1:1 EtOAc-Hexanes) yielded 415 mg (90%) of **280** as an oil. ^{1}H-NMR ($CDCl_3$) δ 1.2-2.6 (m, 9H, cyclopentyl $C\underline{H}_2$ & $C\underline{H}$, 1 benzylic $\underline{H}$, RO$\underline{H}$), 2.90 (d, 1H, J = 7.5 Hz, Ar$C\underline{H}_2$-), 3.86 (s, 4H, $OC\underline{H}_2C\underline{H}_2O$), 3.88 (s, 3H, $OC\underline{H}_3$), 3.99 (s, 3H, $OC\underline{H}_3$), 4.86 (s, 2H, Ar$C\underline{H}_2$OH), 6.7-6.9 (m, 1H, Ar$\underline{H}$), 7.1-7.2 (m, 3H, Ar$\underline{H}$); ^{13}C-NMR ($CDCl_3$) δ 30.2, 35.9, 38.8, 42.5, 56.0, 57.2, 63.0, 64.0, 64.2, 105.4, 117.7, 120.6, 124.7, 126.3, 130.0, 136.6, 139.0, 155.4, 155.7; IR (KBr) cm^{-1} 3460 (RO-H), 3053 (Ar C-H), 2958, 2935 (aliphatic C-H), 2837 (ArOMe), 1624, 1600, 1570, 1460 (Ar C=C); mass spectrum *m/z* 358 (M^+, 100), 341 (31), 127 (90), 99 (20).

1,8-Dimethoxy-3-(3,3-(ethane-1',2'-diyldioxy)-cyclopentylmethyl)naphthalene-2-carboxaldehyde (281). The alcohol **281** (410 mg, 1.14 mmol), dissolved in methylene chloride (5 mL), was added to a solution of Collins reagent prepared from pyridine (1.2 mL, 14 mmol) and CrO_3 (715 mg, 7.15 mmol) in dry methylene chloride (25 mL), and the mixture was stirred for 25 min at

room temperature under a nitrogen atmosphere. The methylene chloride solution was decanted from the precipitated chromium salts and concentrated to 1/4 volume. The chromium precipitate in the reaction flask was washed with ether (2 x 25 mL) and the combined ether solution was added to the methylene chloride fraction. The combined organic solution was filtered, and the filtrate washed with dilute aqueous sodium hydroxide (2 x 25 mL), aqueous sodium bicarbonate (25 mL), and brine, then dried ($MgSO_4$), filtered, and evaporated at reduced pressure to yield 297 mg (73%) of **281** as an oil which was pure by TLC and NMR. ^{1}H-NMR ($CDCl_3$) δ 1.2-2.5 (m, 8H, cyclopentyl $C\underline{H}_2$ & $C\underline{H}$, 1 benzylic $\underline{H}$), 3.12 (dd, 1H, J = 7.2 Hz, J = 5.0 Hz, $ArC\underline{H}_2$-), 3.87 (s, 4H, $OC\underline{H}_2C\underline{H}_2O$), 3.94 (s, 3H, $OC\underline{H}_3$), 4.03 (s, 3H, $OC\underline{H}_3$), 6.88 (dd, 1H, J = 8.0 Hz, J = 1.4 Hz, Ar$\underline{H}$), 7.2-7.5 (m, 3H, Ar$\underline{H}$), 10.70 (s, 1H, Aldehyde $C\underline{H}O$); ^{13}C-NMR ($CDCl_3$) δ 30.2, 35.9, 38.5, 39.4, 42.5, 56.0, 63.9, 64.1, 64.9, 105.9, 117.7, 120.3, 125.9, 129.4, 136.2, 139.3, 149.3, 156.7, 192.8 (C=O); IR (film) cm^{-1} 3050 (Ar C-H), 2940, 2936 (aliphatic C-H), 2840 (ArOMe), 1682 (C=O), 1620, 1596, 1566, 1492, 1460 (Ar C=C); mass spectrum *m/z* 356 (M^+, 31), 127 (100), 99 (19).

5,6-Dimethoxy-2,3,11,11a-tetrahydro-3(1H)-cyclopenta[*b*]anthracenone (282). Dilute perchloric acid (2 mL, 2N) was added to a solution of the aldehyde **281** (297 mg, 0.834 mmol) in THF (12 mL) and water (3 mL) and the reaction stirred at room temperature for 16 hr. Ether (50 mL) was added and the solution washed with aqueous sodium bicarbonate (3 x 15 mL) and brine (15 mL), then dried ($MgSO_4$), filtered, and concentrated to give 240 mg of a yellow solid. Chromato-

graphy of the material on silica gel (20 g, EtOAc) gave 205 mg (84%) of **282** as a yellow-orange solid, which after recrystallization (CH_2Cl_2-Hexanes) had mp 182-186 °C. ^{1}H-NMR ($CDCl_3$) δ 1.3-1.9 (m, 1H, -C$\underline{H}_2$), 2.3-3.5 (m, 6H, A ring-C$\underline{H}_2$ & C$\underline{H}$, benzylic-C$\underline{H}_2$), 3.86 (s, 3H, OC$\underline{H}_3$), 4.00 (s, 3H, OC$\underline{H}_3$), 6.80 (dd, 1H, J = 6.4 Hz, J = 2.4 Hz, Ar$\underline{H}$), 7.2-7.4 (m, 3H, Ar$\underline{H}$ + vinyl $\underline{H}$), 7.80 (d, 1H, J = 2.4 Hz, Ar$\underline{H}$); ^{13}C-NMR ($CDCl_3$) δ 27.8, 36.2, 39.0, 56.0, 63.5, 106.0, 120.5, 122.6, 124.4, 127.5, 135.0, 137.7, 139.6, 156.4, 205.8, 119.1, 124.0 ($\underline{C}$=O); IR (film) cm^{-1} 3156, 3060 (vinyl C-H), 2965, 2935, 2900 (aliphatic C-H), 2840 (ArOMe), 1704 (C=O), 1616 (C=C), 1566, 1464 (Ar C=C); mass spectrum *m/z* 294 (M^+, 100), 266 (8), 251 (11), 238 (10), 223 (9).

5,6-Dimethoxy-3-hydroxy-2,3,11,11a-tetrahydro-1H-cyclopenta[*b*]anthracene (286). A benzene solution of sodium *bis*(2-methoxyethoxy)aluminum hydride (Red-Al, 3.4 M, 150 mL, 0.51 mmol) was added to a magnetically stirred, chilled (0° C) solution of the ketone **282** (76 mg, 0.26 mmol) in dry dimethoxyethane (10 mL). The reaction was continued for 2.5 hours under nitrogen, then quenched by addition of water (1 mL). Ethyl acetate (30 mL) was added and the organic layer washed with water (10 mL), hydrochloric acid (1N, 10 mL), aqueous sodium bicarbonate (10 mL) and brine (10 mL), then dried ($MgSO_4$), filtered, and evaporated at reduced pressure. Chromatography of the residue on silica gel (1 g, CH_2Cl_2 followed by EtOAc) gave 59 mg (77%) of **286** as oil which gave a foam under vacuum. ^{1}H NMR ($CDCl_3$) δ 1.2-3.2 (m, 8H, A ring-C$\underline{H}_2$ & C$\underline{H}$, benzylic-C$\underline{H}_2$, RO$\underline{H}$), 3.82 (s, 3H, OC$\underline{H}_3$), 3.98 (s, 3H, OC$\underline{H}_3$), 4.7-4.9 (m, 1H, C$\underline{H}$OH), 6.78 (t, 1H, J = 4.4 Hz, Ar$\underline{H}$), 7.08 (brd s, 1H,

vinyl H?), 7.2-7.4 (m, 3H, ArH); IR (film) cm^{-1} 3400 (O-H), 3055 (vinyl C-H), 2955, 2934, 2871 (aliphatic C-H), 2836 (ArOMe), 1623 (C=C), 1603, 1568, 1460 (Ar C=C); mass spectrum *m/z* 296 (M^+, 100), 278 (41).

3-Acetoxy-5,6-dimethoxy-2,3,11,11a-tetrahydro-1H-cyclopenta[*b*]anthracene (287). The alcohol **286** (59 mg, 0.20 mmol), acetic anhydride (300 mL), pyridine (300 mL), and dimethylamino pyridine (20 mg) were stirred in dry methylene chloride (10 mL) at room temperature for 16 hr. Ether (30 mL) was added and the solution washed successively with 1N hydrochloric acid (5 mL), aqueous sodium bicarbonate (5 mL) and brine (5 mL), then dried ($MgSO_4$), filtered, and concentrated to yield 68 mg (100%) of **287** as an oil. TLC analysis indicated the product was pure and the ^{1}H-NMR spectrum indicated that the product consisted of an 8:2 mixture of epimeric acetates. ^{1}H-NMR ($CDCl_3$) δ 1.4-3.2 (m, 7 H, A ring-CH_2 & CH, benzylic-CH_2), 2.06 (s, 3H, $COCH_3$), 3.81 (s, 3H, OCH_3), 4.00 (s, 3H, OCH_3), 5.7-5.9 (m, 1H, CHOH), 6.78 (t, 1H, J = 4.5 Hz, ArH), 7.06 (brd s, 1H, vinyl H?), 7.2-7.4 (m, 3H, ArH); ^{13}C-NMR ($CDCl_3$) δ 21.3, 30.3, 32.8, 35.9, 38.4, 56.1, 62.6, 75.6, 105.8, 118.6, 120.5, 122.1, 125.9, 136.4, 137.4, 147.1, 156.2, 170.9 (C=O, acetate); IR (film) cm^{-1} 3057 (vinyl C-H), 2960, 2935, 2873 (aliphatic C-H), 2837 (ArOMe), 1720 (C=O), 1623 (C=C), 1603, 1569, 1460 (Ar C=C)); mass spectrum *m/z* 338 (M^+, 100), 279 (86, M^+-$CH_3CO_2^-$), 278 (73, M^+-CH_3CO_2H).

3-Acetoxy-3a,4-dihydroxy-5,6-dimethoxy-2,3,3a,4,11,11a-hexahydro-1H-cyclopenta[*b*]anthracene (288).

The unsaturated acetate **287** (68 mg, 0.20 mmol), osmium tetraoxide (1 mL, 0.020 M in butanol, 0.020 mmol),and trimethylamine N-oxide dihydrate (33 mg, 0.30 mmol) were stirred together in acetone (8 mL) and water (2 mL) for 5 days at room temperature. Aqueous sodium bisulfite (5 mL) was added and the mixture extracted with ethyl acetate (25 mL). The ethyl acetate solution was washed successively with water (2 x 5 mL) and brine (5 mL), then dried ($MgSO_4$), filtered, and evaporated at reduced pressure, to furnished 75 mg oil. Radial thick layer chromatography of the residue (2 mm, silica gel, 15-60% EtOAc-Hexanes) yielded 44 mg (58%) of **288** as a mixture of isomers. ^{1}H-NMR ($CDCl_3$) δ 2.00 (s, 3H, $COC\underline{H}_3$), 3.91 (s, 3H, $OC\underline{H}_3$), 4.00 (s, 3H, $OC\underline{H}_3$), 4.6 (brd s, 1H, RO<u>H</u>?), 5.12 (brd t, 1H, J = 6 Hz, C<u>H</u>OAc), 5.46 (s, 1H, ArC<u>H</u>OH), 6.82 (t, 1H, J = 5.0 Hz, Ar<u>H</u>), 7.2-7.5 (m, 3H, Ar<u>H</u>); mass spectrum *m/z* 372 (M^+, 16), 312 (M^+- CH_3CO_2H, 13), 294 (M^+- CH_3CO_2H - H_2O, 100).

3-Acetoxy-3a,4-(isopropylidenedioxy)-5,6-dimethoxy-2,3,3a,4,11,11a-hexahydro-1H-cyclopenta-[*b*]anthracene (289a). The diol **288** (44 mg, 0.118 mmol), 2,2-dimethoxypropane (100 mL, 0.81 mmol), and pyridinium *p*-toluene sulfonate (10 mg) were stirred in benzene (20 mL) at reflux for 6 hours and then at room temperature for 60 hr. The reaction was washed with dilute aqueous sodium bicarbonate (2 x 10 mL), then dried ($MgSO_4$), filtered, and evaporated at reduced pressure to yield 44 mg of material. Chromatography on silica gel (2 g, 0-100% EtOAc-CH_2Cl_2) gave 18 mg (37%) of **289a** as a mixture of isomers. ^{1}H-NMR ($CDCl_3$) δ 1.26 (s, 3H, $C\underline{H}_3$),

1.51 (s, 3H, $C\underline{H}_3$), 2.00 (s, $COC\underline{H}_3$), 2.08 (s, $COC\underline{H}_3$), 3.92 (s, $OC\underline{H}_3$), 3.96 (s, $OC\underline{H}_3$), 4.01 (s, $OC\underline{H}_3$), 5.0-5.6 (m, 2H, $C\underline{H}OH$), 6.6-7.0 (m, 1H, $Ar\underline{H}$), 7.1-7.5 (m, 3H, $Ar\underline{H}$); mass spectrum *m/z* 412 (M^+, 100), 312 (83), 295 (35), 294 (38).

3a,4-(Isopropylidenedioxy)-5,6-dimethoxy-3-hydroxy-2,3,3a,4,11,11a-hexahydro-1H-cyclopenta-[*b*]anthracene (289b). The acetate **289a** (18 mg, 0.044 mmol) and potassium carbonate (30 mg) were stirred together in methanol (10 mL) and water (1 mL) at room temperature for 5 hr. The solids were filtered off and the methanol evaporated. The residue was dissolved in ethyl acetate (15 mL) and washed with water (5 mL) and aqueous sodium bicarbonate (5 mL), then dried ($MgSO_4$), and filtered. Evaporation of the ethyl acetate at reduced pressure gave 14 mg (87%) of **289b** as an oil which was not further purified. ^{1}H-NMR ($CDCl_3$) δ 1.25 (s, 6H, $C\underline{H}_3$), 3.95 (s, 3H, $OC\underline{H}_3$), 3.99 (s, 3H, $OC\underline{H}_3$), 6.6-7.0 (m, 1H, $Ar\underline{H}$), 7.1-7.5 (m, 3H, $Ar\underline{H}$); mass spectrum *m/z* 370 (M^+, 100), 312 (32), 296 (20), 255 (42).

3a,4-(Isopropylidenedioxy)-5,6-dimethoxy-2,3,3a,4,11,11a-hexahydro-3(1H)-cyclopenta[*b*]anthracenone (290). A solution of the crude alcohol **289b** (14 mg) in methylene chloride (3 mL) was added to a solution of CrO_3 (25 mg) and pyridine (36 mL) in dry methylene chloride (4 mL) and stirred at room temperature for 30 min. Ether (10 mL) was added and the solution was concentrated to 1/4 volume. Additional ether (15 mL) was added and the suspension was

filtered. The filtrate was washed with water (5 mL) and aqueous sodium bicarbonate (5 mL), then dried ($MgSO_4$), filtered, and evaporated at reduced pressure. Chromatography of the residue on silica gel (1 g) with methylene chloride yielded 13 mg. (81% from **289a**) of **290**. ^{1}H-NMR ($CDCl_3$) δ 1.18 (s, 6H, $C\underline{H}_3$), 3.88 (s, 3H, $OC\underline{H}_3$), 3.92 (s, 3H, $OC\underline{H}_3$), 6.6-6.8 (m, 1H, Ar$\underline{H}$), 7.1-7.5 (m, 3H, Ar$\underline{H}$).

III. Isocoumarins

Condensation of phthalaldehydic acids with nitro alkanes, ***Method A: Sodium Hydroxide.***

3-Nitromethyl-1(3H)-isobenzofuranone (359a). Aqueous sodium hydroxide (10 N, 8.4 mL, 84 mmol) was added slowly to a chilled (0 °C) solution of phthalaldehydic acid (**27a**) (5.00 g, 33.3 mmol) and nitromethane (**28a**) (2.2 mL, 40 mmol) in methanol (50 mL). The solution was allowed to warm to room temperature and then stirred for 2.5 hr. Acetic acid (5 mL) and then hydrochloric acid (60 mL, 6N) were added. The resulting mixture was chilled (0 °C) and the precipitate collected by filtration to yield 5.2 g (81%) of **29a** as a white crystals. Recrystallization (CH_2Cl_2-hexanes) of an analytical sample gave mp 126-128 °C (lit.[131] mp 129-131 °C). ^{1}H-NMR ($CDCl_3$) δ 4.75 (dd, 1H, J = 7.04 Hz, J = 14.08 Hz, $C\underline{H}NO_2$), 4.80 (dd, 1H, J = 4.84 Hz, J = 14.08 Hz, $C\underline{H}NO_2$), 6.15 (dd, 1H, J = 4.84 Hz, J = 7.04 Hz, Ar-C$\underline{H}$), 7.44-8.08 (m, 4H, Ar$\underline{H}$).

3-(1-Nitroethyl)-1(3H)-isobenzofuranone (359b). To a solution of phthalaldehydic acid **357a** (3.6 g, 24 mmol) and nitroethane (2.2 mL, 24 mmol) dissolved in ethanol (40 mL) was added aqueous sodium hydroxide (10 N, 4.3 mL, 43 mmol). The reaction was stirred at room temperature for 2 days. The reaction was quenched by addition of acetic acid (3 mL) and then acidified with dilute hydrochloric acid. The mixture was extracted with ether (3 x 50 mL) and the combined ether solution was washed with water (2 x 50 mL) and brine, then dried ($MgSO_4$), filtered, and concentrated. The residue was dissolved in methylene chloride (30 mL) and treated with trifluoroacetic acid (0.5 mL) at room temperature for 2 hours. The solution was washed with water (50 mL) and brine, then dried ($MgSO_4$), filtered, and evaporated under reduced pressure.

Chromatography of the residue on silica gel (CH_2Cl_2) gave 3.52 g (70%) of **359b** as an oil. Analysis of a ^{1}H-NMR spectrum of the material indicated that it was a 2:1 mixture of diastereoisomers contaminated with about 10-20% of 3-ethoxyphthalide (**364**). ^{1}H-NMR ($CDCl_3$) δ 1.46 (d, 3H, J = 6.6 Hz, C<u>H</u>$_3$, major isomer), 1.67 (d, 3H, J = 7.0 Hz, C<u>H</u>$_3$, minor isomer), 4.80-5.16 (m, 1H, C<u>H</u>NO_2), 5.95 (d, 1H, J = 8.3 Hz, Ar-C<u>H</u>, minor isomer), 6.13 (d, 1H, J = 4.0 Hz, Ar-C<u>H</u>-, major isomer), 7.48-8.06 (m, 4H, Ar<u>H</u>); ^{13}C-NMR ($CDCl_3$) δ (11.9, 14.4, C<u>H</u>$_3$), 79.3 (<u>C</u>HNO_2), (83.0, 83.3, Ar-<u>C</u>H), (122.1, 122.9), 125.8, 130.2, (134.4, 134.8), (143.8, 144.7) (Ar<u>C</u>), (168.6, 168.9, <u>C</u>=O); IR (film) cm^{-1} 1772 (C=O), 1557, 1362 (NO_2) cm^{-1}; mass spectrum *m/z* 161 (M^+-NO_2, 13), 160 (75), 133 (100), 105 (25).

3-(1-Nitropropyl)-1(3H)-isobenzofuranone (359c). To a solution of phthalaldehydic acid **357a** (3.99 g, 26.6 mmol) and nitropropane **363c** (3.03 mL, 33.3 mmol), in ethanol (25 mL) was added aqueous sodium hydroxide (10 N, 6.7 mL, 67 mmol) and piperidine (10 drops). The reaction was stirred at room temperature for 7 days. The reaction was quenched with acetic acid (5 mL) and acidified with dilute hydrochloric acid (10 mL, 1N). The mixture was extracted with ether (3 x 50 mL) and the combined ether extracts were washed with water, then dried ($MgSO_4$), filtered, and evaporated at reduced pressure. The residue was dissolved in methylene chloride (50 mL) and treated with trifluoro-acetic acid (0.3 mL) at room temperature for 1 hour. The solution was washed with water, then dried ($MgSO_4$), filtered, and evaporated at reduced pressure. Chromatography of the residue on silica gel (CH_2Cl_2) gave 2.79 g (48%) of **359c** as an oil. The ^{1}H-NMR spectrum of the material indicated that it was a mixture of diastereoisomers contaminated with about 20% of 3-ethoxyphthalide (**364**). ^{1}H-NMR ($CDCl_3$) δ 1.04, 1.08 (t, 3H, J = 7.3 Hz, C$\underline{H}_3$), 1.9-2.4 (m, 2H, C$\underline{H}_2$), 4.4-4.9 (m, 1H, C$\underline{H}NO_2$), 5.78, 5.84 (d, 1H, J = 6.2 Hz, Ar-C$\underline{H}$), 7.3-8.0 (m, 4H, Ar$\underline{H}$).

3-Ethoxy-1(3H)-isobenzofuranone (364). Phthalaldehydic acid **357a** (0.5 g) was stirred in ethanol (10 mL) at room temperature for 2.5 days. Evaporation at reduced pressure yielded **364** as an oil. ^{1}H-NMR ($CDCl_3$) δ 1.33 (t, 3H, J = 7.04 Hz, C$\underline{H}_3$), 3.88 (dq, 1H, J = 14.08 Hz, J = 7.04 Hz, C$\underline{H}_2$), 3.98 (dq, 1H, J = 14.08 Hz, J = 7.04 Hz, C$\underline{H}_2$), 6.37 (s,

1H, Ar-C<u>H</u>), 7.4 - 8.0 (m, 4H, Ar<u>H</u>); ^{13}C-NMR ($CDCl_3$) δ 15.1 ($OCH_2\underline{C}H_3$), 65.8 ($O\underline{C}H_2CH_3$), 102.3 (Ar<u>C</u>H$(OR)_2$), 123.4, 125.4, 130.7, 134.3 (Ar<u>C</u>); IR (film) 1772 (C=O).

Method B: Triethylamine, (General procedure). The phthalaldehydic acid (6 mmol), the nitro compound (1.4 equiv), and triethylamine (1.6 equiv) were stirred together in dimethyl sulfoxide (6 mL) at room temperature for 1-2 days. The reaction was quenched with acetic acid (0.8 mL), then acidified with hydrochloric acid (12N, 3 mL) and stirred for 30-60 min. Brine (25 mL) was added and the resulting mixture extracted with ethyl acetate (2 x 50 mL). The organic layer was washed with brine (4 x 20 mL), then dried ($MgSO_4$), filtered, and evaporated at reduced pressure. Chromatography of the residue on silica gel (20 g, CH_2Cl_2) furnished pure product.

3-(1-Nitroethyl)-1(3H)-isobenzofuranone (359b). The nitro lactone **359b**, prepared from phthalaldehydic acid **357a** and nitroethane, was isolated in 86% yield as an oil which solidified on standing. A ^{1}H-NMR spectrum indicated a mixture of diastereoisomers. ^{1}H-NMR ($CDCl_3$) δ (major isomer) 1.46 (d, 3H, J = 6.59 Hz, C<u>H</u>$_3$), (minor isomer) 1.67 (d, 3H, J = 7.04 Hz, C<u>H</u>$_3$), 4.80-5.16 (m, 1H, C<u>H</u>NO_2), 6.13 (d, 1H, J = 3.96 Hz, Ar-C<u>H</u>), 7.48-8.06 (m, 4H, Ar<u>H</u>); ^{13}C-NMR ($CDCl_3$) δ (11.9, 14.4, C<u>H</u>$_3$), 79.3, (<u>C</u>HNO_2), (83.0, 83.3, Ar<u>C</u>H), (122.1, 122.9), 125.8, 130.2, (134.4, 134.8), (143.8, 144.7) (Ar<u>C</u>), (168.6, 168.9, <u>C</u>=O); IR (film) cm^{-1} 1772 (C=O),

1557, 1362 (NO_2) cm^{-1}; mass spectrum *m/z* 161 (M^+-NO_2, 13), 160 (75), 133 (100), 105 (25).

3-(1-Nitropropyl)-1(3H)-isobenzofuranone (359c). The nitro lactone **359c**, prepared from phthalaldehydic acid **357a** and nitropropane, was isolated in 69% yield as an oil which crystallized on standing. Recrystallization (CH_2Cl_2-hexanes) of the material gave a single diastereoisomer as white needles with mp 76-79 °C. ^{1}H-NMR ($CDCl_3$) δ 1.07 (t, 3H, J = 7.3 Hz, C<u>H</u>$_3$), 1.80-2.42 (m, 2H, C<u>H</u>$_2$), 4.60-4.88 (m, 1H, C<u>H</u>NO_2), 5.83 (d, 1H, J = 6.2 Hz, Ar-C<u>H</u>), 7.48-8.04 (m, 4H, Ar<u>H</u>); ^{13}C-NMR ($CDCl_3$) δ 10.1 (<u>C</u>H_3), 22.8 (<u>C</u>H_2CH_3), 78.8 (<u>C</u>HNO_2), 90.2 (Ar-<u>C</u>H), 123.0, 126.2, 126.3, 130.4, 134.4, 143.9 (Ar<u>C</u>), 168.5 (C=O); IR (film) cm^{-1} 1773 (C=O), 1557, 1375 (NO_2); mass spectrum *m/z* 175 (M^+ -NO_2, 14), 174 (50), 159 (20), 146 (6), 133 (100).

Anal. Calcd. for $C_{11}H_{11}O_4N$: C, 59.72; H, 5.01; N, 6.33%). Found: C, 59.60; H, 5.08; N, 6.29.

3-(Phenylnitromethyl)-1(3H)-isobenzofuranone (359d). The nitro lactone **359d** was prepared from phthalaldehydic acid **357a** and phenylnitromethane. The initial product was recrystallized (CH_2Cl_2-hexanes) to give **359d** in 65% yield as white crystals with mp. 148-151 °C. ^{1}H-NMR ($CDCl_3$) δ 5.36 (d, 1H, J = 10.11 Hz, C<u>H</u>NO_2), 6.19 (d, 1H, J = 7.03 Hz, Ar<u>H</u>), 6.39 (d, 1H, J = 10.11 Hz, Ar-C<u>H</u>), 7.24-7.68 (m, 7H, Ar<u>H</u>), 7.80-8.00 (m, 1H, Ar<u>H</u>); ^{13}C-NMR ($CDCl_3$) δ 92.3 (Ar-<u>C</u>H), 127.4, 127.7, 128.0, 129.1, 129.7, 132.6, 133.8, 134.9, 138.5 (Ar<u>C</u>), 172.3 (C=O); IR (film) cm^{-1} 1773

(C=O), 1560, 1367 (NO_2); mass spectrum *m/z* 223 ($M-NO_2^+$, 32), 195 (23), 133 (100).

Anal. Calcd. for $C_{15}H_{11}O_4N$: C, 66.91, H, 4.12; N, 5.20). Found: C,66.80; H, 4.12; N, 5.20.

3-(1-Nitroethyl)-7-methoxy-1(3H)-isobenzofuranone (359e). The nitro lactone **359e**, prepared from phthalaldehydic acid **357b** and nitroethane, was isolated in 90% yield as an oil which solidified on standing. A ^{1}H-NMR spectrum of the material indicated it was a 1:1 mixture of diastereoisomers. ^{1}H-NMR ($CDCl_3$) δ 1.54 (t, 3H, J = 6.38 Hz, $C\underline{H}_3$), 4.01 (s, 3H, $OC\underline{H}_3$), 4.60-5.12 (m, 1H, $C\underline{H}NO_2$), 5.86, 5.98 (d, 1H, combined, J = 5.7 Hz, Ar-C<u>H</u>), 6.90-7.16 (m, 2H, Ar<u>H</u>), 7.56-7.80 (m, 1H, Ar<u>H</u>); ^{13}C-NMR ($CDCl_3$) δ 11.9 ($\underline{C}H_3$), 14.1 ($\underline{C}H_3$), 55.9 ($O\underline{C}H_3$), 78.2 (Ar-<u>C</u>H), 78.3 (Ar-<u>C</u>H), 83.1 ($\underline{C}HNO_2$), 83.2 ($\underline{C}HNO_2$), 112.1, 113.5, 114.4, 136.8, 137.2, 145.4, 147.4, 158.8 (Ar<u>C</u>), 166.6, 166.9 (<u>C</u>=O); IR (film) cm^{-1} 2845 ($ArOCH_3$), 1773 (C=O), 1555, 1362 (NO_2).

3-(4-Methoxyphenyl)-7-methoxy-1(3H)-isobenzofuranone (359f). The nitro lactone **359f**, prepared from phthalaldehydic acid **357b** and 4-methoxyphenylnitromethane **363e**, was isolated in 45% yield as an oil which solidified on standing. A ^{1}H-NMR spectrum of the material indicated it was an 8:2 mixture of diastereoisomers. ^{1}H-NMR ($CDCl_3$), δ 3.85 (s, 3H, $OC\underline{H}_3$), 3.95 (s, 3H, $OC\underline{H}_3$), 5.25 (d, 1H, J = 10.12 Hz, $C\underline{H}NO_2$), 5.29 (d, 1H, J = 7.48 Hz, Ar<u>H</u>), 6.23 (d, 1H, J = 10.12

Hz, Ar-C<u>H</u>), 6.8 - 7.2 (m, 3H, Ar<u>H</u>), 7.2 - 7.7 (m, 3H, Ar<u>H</u>); IR (KBr) cm^{-1}, 2843 (ArOMe), 1772 (C=O), 1612, 1601, 1563, 1515, 1488 (Ar C=C).

3-(3,4-Dimethoxyphenyl)-7-methoxy-1(3H)-isobenzofuranone (359g). The nitro lactone **359g**, prepared from phthalaldehydic acid **357b** and 3,4-dimethoxyphenylnitromethane **363f**, was isolated in 40% yield as an oil which solidified on standing. A ^{1}H-NMR spectrum of the material indicated it was an 8:2 mixture of diastereoisomers. ^{1}H-NMR ($CDCl_3$), δ 3.89 (s, 3H, OC<u>H</u>$_3$), 3.95 (s, 3H, OC<u>H</u>$_3$), 3.98 (s, 3H, OC<u>H</u>$_3$), 5.25 (d, 1H, J = 10.12 Hz, C<u>H</u>NO_2), 5.84 (d, 1H, J = 7.91 Hz, Ar<u>H</u>), 6.26 (d, 1H, J = 10.12 Hz, Ar-C<u>H</u>), 6.8 - 7.6 (m, 5 H, Ar<u>H</u>); IR (KBr) cm^{-1} 2843 (ArOMe), 1773 (C=O), 1603, 1562, 1518, 1488, 1464 (Ar C=C).

Reduction with Sodium Borohydride. (General procedure). The nitro lactone (4.6 mmol) was dissolved in dimethyl sulfoxide (10 mL) and placed in a water bath (25° C). Sodium borohydride (3.5 mmol) was added slowly in small portions to prevent excessive frothing and the resulting mixture stirred for 1 hour at room temperature. The reaction was quenched by addition of acetic acid (0.9 mL), water (25 mL) and hydrochloric acid (12N, 2.3 mL). The reaction was extracted with ethyl acetate (3 x 20 mL), and the combined ethyl acetate solution washed with water (3 x 15 mL) and brine, then dried ($MgSO_4$), filtered and evaporated. Chromatography on silica gel (20 g, CH_2Cl_2 then EtOAc) yielded pure product.

2-(2-Nitroethyl)benzoic acid (360a); The acid **360a** was isolated in 93% yield as a pale yellow solid with mp 127-129 °C. ^{1}H-NMR ($CDCl_3$) δ 3.71 (t, 2H, J = 7.0 Hz, Ar$\underline{C}H_2$), 4.74 (t, 2H, J = 7.0 Hz, $\underline{C}HNO_2$), 7.20-7.80 (m, 3H, Ar$\underline{H}$), 8.08-8.24 (dd, 1H, J =8 Hz, J = 2 Hz, Ar$\underline{H}$); IR (film) cm^{-1} 3400-2400 (CO_2H), 1693 (C=O), 1554, 1379 (NO_2).

2-(2-Nitropropyl)benzoic acid (360b); The acid **360b** was isolated in 77% yield as a white solid with mp 118-120 °C. ^{1}H-NMR ($CDCl_3$) δ 1.63 (d, 3H, J = 7.0 Hz, $C\underline{H}_3$), 3.40-3.80 (m, 2H, Ar$\underline{C}H_2$), 4.70-5.18 (m, 1H, $\underline{C}HNO_2$), 7.10-7.60 (m, 3H, Ar$\underline{H}$), 8.16 (dd, 1H, J = 8 Hz J = 2 Hz, Ar$\underline{H}$); ^{13}C-NMR ($CDCl_3$) δ 19.5 ($\underline{C}H_3$), 40.0 (Ar$\underline{C}H_2$), 84.7 ($\underline{C}HNO_2$), 127.4, 127.8, 132.2, 132.4, 133.6, 138.9 (Ar$\underline{C}$), 172.4 ($\underline{C}$=O); IR (film) cm^{-1} 3400-2400 (CO_2H), 1692 (C=O), 1550, 1362 (NO_2); mass spectrum (FAB) *m/z* 210 (M^++1, 11), 194 (100), 192 (16), 179 (47), 176 (42), 163 (31), 145 (27), 133(77).

2-(2-Nitrobutyl)benzoic acid (360c); Recrystallization of the crude product (CH_2Cl_2-hexanes) yielded 0.77 g (70%) of **360c** as white crystals with mp 134-136 °C. ^{1}H-NMR ($CDCl_3$) δ 1.03 (t, 3H, J = 7.3 Hz, $CH_2C\underline{H}_3$), 1.70-2.30 (m, 2H, $C\underline{H}_2CH_3$, 3.36 (dd, 1H, J = 9.2 Hz, J = 14.0 Hz, Ar$C\underline{H}_2$), 3.76 (dd, 1H, J = 4.0 Hz, J = 14.0 Hz, Ar$C\underline{H}_2$), 4.64-5.00 (m, 1H, $C\underline{H}NO_2$), 7.12-7.64 (m, 3H, Ar$\underline{H}$), 8.17 (dd, 1H, J = 2.2 Hz, J = 7.0 Hz, Ar$\underline{H}$); ^{13}C-NMR ($CDCl_3$) δ 10.2 ($\underline{C}H_3$), 27.5 ($\underline{C}H_2CH_3$), 38.6 (Ar$\underline{C}H_2$), 91.4 ($\underline{C}HNO_2$), 127.4, 127.8, 132.2, 132.5, 133.8, 139.1 (Ar$\underline{C}$), 172.8 (C=O); IR (film) cm^{-1} 3400-2400 (CO_2H), 1691 (C=O), 1550, 1375 (NO_2); mass spectrum (FAB) *m/z*

177 (M^+-NO_2, 22), 176 (70), 159 (30), 158 (27), 147 (47), 135 (100), 131 (55).

Anal. Calcd. for $C_{11}H_{13}O_4N$: C, 59.19; H, 5.87, N, 6.28. Found C, 59.28; H, 5.87; N, 6.19.

2-(2-Phenyl-2-nitroethyl)benzoic acid (360d). Recrystallization of the crude product (CH_2Cl_2-hexanes) yielded 0.64 g (85%) of **360d** as white crystals with mp 150-153 °C. ^{1}H-NMR ($CDCl_3$) δ 3.80-4.16 (m, 2H, ArCH_2), 5.84-6.04 (m, 1H, $CHNO_2$), 7.12-7.60 (m, 8H, ArH), 8.18-8.24 (m, 1H, ArH); ^{13}C-NMR ($CDCl_3$) δ 39.7 (ArCH_2), 92.3 ($CHNO_2$), 127.4, 127.7, 128.0, 129.1, 129.7, 132.6, 133.8, 134.9, 138.5 (ArC), 172.3 (C=O); IR (KBr) cm^{-1} 3400-2500 (CO_2H), 1689 (C=O), 1553, 1369 (NO_2); mass spectrum *m/z* 225 (M^+-NO_2, 48), 207 (100), 194 (14), 178 (39), 118 (100).

Anal. Calcd. for $C_{15}H_{13}O_4N$: C, 66.41; 4.83; N, 5.16. Found: C, 66.69; H, 5.01; N, 4.95.

2-(2-Nitropropyl)-7-methoxybenzoic acid (360e). The acid **360e** was isolated in 95% yield as an oil. ^{1}H-NMR ($CDCl_3$) δ 1.58 (d, 3H, J = 6.6 Hz, CH_3), 3.24-3.40 (m, 2H, ArCH_2), 3.92 (s, 3H, OCH_3), 4.72-5.16 (m, 1H, $CHNO_2$), 6.72-7.02 (m, 2H, ArH), 7.22-7.48 (m, 1H, ArH); ^{13}C-NMR ($CDCl_3$) δ 19.1 (CH_3), 39.2 (ArCH_2), 56.3 (OCH_3), 84.3 ($CHNO_2$), 110.8, 120.7, 123.4, 132.0, 136.9, 157.5 (ArC), 170.2 (C=O); IR (KBr) cm^{-1} 3500-2500 (CO_2H), 2842 ($ArOCH_3$), 1731, 1701 (C=O), 1551, 1360 (NO_2).

2-(2-(4-Methoxyphenyl)-2-nitroethyl)-7-methoxybenzoic acid (360f). A modified procedure was employed. Aqueous sodium hydroxide (1N, 2 mL) was added to the reaction prior to the addition of sodium borohydride. The acid **360f** was isolated in 73% yield as a solid. ^{1}H-NMR ($CDCl_3$) δ 3.78 (s, 3H, OCH_3), 3.91 (s, 3H, OCH_3), 3.4-4.0 (m, 2H, $ArCH_2$), 5.76-5.98 (m, 1H, $CHNO_2$), 6.70-7.04 (m, 4H, ArH), 7.20-7.52 (m, 3H, ArH); ^{13}C-NMR ($CDCl_3$) δ 39.0 (CH_3), 55.2 (OCH_3), 56.4 (OCH_3), 91.6 ($CHNO_2$), 110.9, 114.2, 120.8, 123.9, 126.8, 128.9, 132.1, 137.1, 157.6, 160.5 (ArC), 169.9 (C=O).

2-(2-(3,4-Dimethoxyphenyl)-2-nitroethyl)-7-methoxybenzoic acid (360g). A modified procedure was employed. Aqueous sodium hydroxide (1N, 2 mL) was added to the reaction prior to the addition of sodium borohydride. The acid **360g** was isolated in 81% yield as a solid. ^{1}H-NMR ($CDCl_3$) δ 3.86 (s, 3H, OCH_3), 3.89 (s, 3H, OCH_3), 3.93 (s, 3H, OCH_3), 3.36-4.00 (m, 2H, $ArCH_2$), 5.76-6.00 (m, 1H, $CHNO_2$), 6.72-7.16 (m, 5H, ArH), 7.20-7.48 (m, 1H, ArH); ^{13}C-NMR ($CDCl_3$) δ 39.0 (CH_3), 55.9 (OCH_3), 56.3 (OCH_3), 91.8 ($CHNO_2$), 110.3, 110.9, 111.1, 120.3, 123.8, 127.0, 132.1, 136.9, 149.1, 150.0, 157.6 (ArC), 170.0 (C=O).

2-(2-Oxopropyl)benzoic acid (361b). A solution of the nitro acid **360b** (971 mg, 4.65 mmol) and sodium methoxide (501 mg, 9.3 mmol) in methanol (20 mL) was added to a vigorously stirred solution of $TiCl_3$ (14.3 mL, 18.6 mmol, 20% in 6N hydrochloric acid) and ammonium acetate (8.6 g, 111.5 mmol) in water (30 mL) at room temperature. The

initial purple colored solution became a blue grey suspension. The reaction was stirred for 1.5 hr, then diluted with water (70 mL) and acidified with 12M hydrochloric acid to pH 1. Sodium chloride (1 gm) was added and the mixture was extracted with ether (100 mL). The ether layer was washed with water (4 x 30 mL) and brine (30 mL), then dried ($MgSO_4$), filtered, and evaporated at reduced pressure. Chromatography of the residue on silica gel (50 g, CH_2Cl_2 then EtOAc) gave 593 mg (72%) of 361b as a pale brown solid. ^{1}H-NMR ($CDCl_3$) δ 2.16 (brd s, 3H, $COC\underline{H}_3$), 3.96 (brd s, 2H, $ArC\underline{H}_2CO$), 7.1-7.7 (m, 3H, Ar$\underline{H}$), 8.0-8.2 (m, 1H, Ar$\underline{H}$); IR ($CDCl_3$) cm^{-1} 3600-2400 (CO_2H), 1700 (C=O); mass spectrum (FAB) *m/z* 179 (M^++1, 87), 161 (100), 135 (29), 133 (18), 119 (40).

Preparation of Isocoumarins.

Method A: Titanium trichloride, (General procedure). A solution of the nitro acid **360** (4.65 mmol) and sodium methoxide (9.3 mmol) in THF (6 mL) was added to a solution of $TiCl_3$ (18.6 mmol, 20% in aqueous 6N HCL) and ammonium acetate (111.5 mmol) in water (20 mL) at room temperature under a nitrogen atmosphere. The reaction was stirred 1.0-1.5 hr, at which time, the initial purple color faded. The solution was acidified with 12N hydrochloric acid to pH 1 and extracted with ethyl acetate (2 x 75 mL). The combined ethyl acetate extracts were washed with water (2 x 40 mL) and brine (25 mL), then dried ($MgSO_4$), filtered, and concentrated. The residue was dissolved in an ethyl acetate (10 mL) containing perchloric acid (.01M) and acetic anhydride (1M). The reaction was stirred for 0.5-1.0 hr at room temperature. Ether (30 mL) was

added and the solution was washed with aqueous bicarbonate (3 x 20 mL), water (20 mL), and brine (10 mL), then dried ($MgSO_4$), filtered, and evaporated under reduced pressure. Chromatography on silica gel (5-20 g, CH_2Cl_2) furnished pure **363**.

1(H)-2-Benzopyran-1-one (363a). A modified procedure was employed. The perchloric acid solution was heated at reflux for .5 hr. The isocoumarin **363a** was isolated in 20% yield as a pale yellow low melting solid (lit.[148] mp 45-46 °C). ^{1}H-NMR ($CDCl_3$) δ 6.49 (d, 1H, J = 5.7 Hz, vinyl H), 7.28 (d, 1H, J = 5.7 Hz, vinyl H), 7.2-8.0 (m, 3H, ArH), 8.31 (brd d, 1H, J = 7.5 Hz, ArH). IR (film) cm^{-1} 1728 (C=O), 1638 (C=C). Mass spectrum, *m/z* 146 (M^+, 39), 118 (100), 97 (59).

3-Methyl-1(H)-2-benzopyran-1-one (363b). The isocoumarin **363b** was isolated in 52% yield as a pale yellow solid with mp 66-69 °C (hexanes) (lit.[149] mp 71-72 °C). ^{1}H-NMR ($CDCl_3$) δ 2.28 (s, 3H, CH_3), 6.26 (s, 1H, vinyl H), 7.2-7.8 (m, 3H, ArH), 8.24 (brd d, 1H, J = 8.4 Hz, ArH); ^{13}C-NMR ($CDCl_3$) δ 19.4 (CH_3), 103.3, 119.7, 124.7, 127.3, 129.2, 134.5, 137.4, 154.3 (ArC), 162.7 (C=O); IR ($CDCl_3$) cm^{-1} 1728 (C=O), 1663 (C=C); Mass spectrum, *m/z* 160 (M^+,100), 145 (M^+-CH_3, 27), 134 (36), 118 (43), 105 (32).

Anal. Calcd. for $C_{10}H_8O_2$: C, 74.99; H, 5.03. Found: C,74.75; H, 5.06.

3-Ethyl-1(H)-2-benzopyran-1-one (363c). The isocoumarin **363c** was isolated in 43% yield as a pale yellow solid with mp 66-70 °C (benzene-hexanes) (lit.[150] mp 72-73 °C). ^{1}H-NMR ($CDCl_3$) δ 1.27 (t, 3H, J = 7.5 Hz, $CH_2C\underline{H}_3$), 2.56 (q, 2H, J = 7.5 Hz, $C\underline{H}_2CH_3$), 6.24 (s, 1H, vinyl H), 7.3-7.8 (m, 3H, ArH), 8.22 (brd d, 1H, J = 8.4 Hz, ArH); ^{13}C-NMR ($CDCl_3$) δ 11.1 ($CH_2\underline{C}H_3$), 26.6(, $\underline{C}H_2CH_3$), 101.9, 120.1, 125.0, 127.4, 129.4, 134.6, 137.6, 159.4 (Ar<u>C</u>), 162.9 (<u>C</u>=O); IR ($CDCl_3$) cm^{-1} 1724 (C=O), 1656 (C=C); Mass spectrum, *m/z* 174 (M^+, 100), 159 (12), 145 (44), 118 (46), 105 (35).

Anal. Calcd. for $C_{11}H_{10}O_2$: C, 75.84, H, 5.79. Found: C, 74.96; H, 5.89.

3-Phenyl-1(H)-2-benzopyran-1-one (363d). The isocoumarin **363d** was isolated in 32% yield as a pale yellow solid with mp 84-85 °C (benzene-hexanes) (lit.[151] mp 91-92 °C). ^{1}H-NMR ($CDCl_3$) δ 6.93 (s, 1H, vinyl H), 7.3-8.0 (m, 8H, ArH), 8.2-8.4 (m, 1H, ArH); ^{13}C-NMR ($CDCl_3$) δ 101.7, 120.5, 125.2, 125.9, 128.0, 128.7, 129.5, 129.9, 131.9, 134.8, 137.5, 153.6 (Ar<u>C</u>), 162.1 (<u>C</u>=O); IR ($CDCl_3$) cm^{-1} 1729 (C=O), 1638 (C=C); Mass spectrum, *m/z* 222 (M^+, 100), 194 (76), 165 (52), 105 (30).

Anal. Calcd. for $C_{15}H_{10}O_2$: C, 81.07; H, 4.54. Found: C, 80.92; H, 4.75.

3-Methyl-7-methoxy-1(H)-2-benzopyran-1-one (363e). The isocoumarin **363e** was isolated in 27% yield as a pale yellow solid with mp 105-108 °C (benzene-hexanes). ^{1}H-NMR ($CDCl_3$) δ 2.22 (s, 3H, $C\underline{H}_3$), 3.98 (s, 3H, $OC\underline{H}_3$), 6.14 (s, 1H, vinyl H), 6.86-7.00 (m, 2H, ArH), 7.44-7.50 (m, 1H, ArH); ^{13}C-NMR ($CDCl_3$) δ 19.1 ($\underline{C}H_3$), 56.0 ($O\underline{C}H_3$), 103.3, 109.2, 114.9, 116.8, 135.4, 136.9, 140.4, 154.7 (Ar<u>C</u>), 161.3 (<u>C</u>=O); IR ($CDCl_3$)

cm^{-1} 2842 (ArOMe), 1728 (C=O), 1669 (C=C); Mass spectrum, *m/z* 190 (M^+, 59), 175 (9), 161 (73).

Anal. Calcd. for $C_{11}H_{10}O_3$: C, 69.46; H, 5.30. Found: C, 69.18; H, 5.35.

3-(4-Methoxyphenyl)-7-methoxy-1(H)-2-benzopyran-1-one (363f). The isocoumarin **363f** was isolated in 27% yield as a pale yellow solid with mp 143-146 °C (benzene-hexanes). ^{1}H-NMR ($CDCl_3$) δ 3.82 (s, 3H, $OC\underline{H}_3$), 3.97 (s, 3H, $OC\underline{H}_3$), 6.68 (s, 1H, vinyl $\underline{H}$), 6.70-7.04 (m, 4H, Ar$\underline{H}$), 7.40-7.84 (m, 3H, Ar$\underline{H}$); ^{13}C-NMR ($CDCl_3$) δ 55.4 ($O\underline{C}H_3$), 56.3 ($O\underline{C}H_3$), 100.2, 109.4, 113.9, 114.2, 117.8, 124.5, 126.9, 135.7, 140.9, 154.0 (Ar$\underline{C}$), 161.1, 161.7 ($\underline{C}$=O); Mass spectrum, *m/z* 282 (M^+, 100), 254 (74), 239 (22), 211 (27).

Anal. Calcd. for $C_{16}H_{14}O_4$: C, 71.10; H, 5.22. Found: C, 71.91; H, 5.14.

***Method B*: *Nef Reaction*,** (General procedure). A solution of the nitro acid **360** (972 mg, 3.60 mmol) in aqueous sodium hydroxide (1N, 15 mL) and methanol (2 mL) was added dropwise to a chilled (0 °C) solution of sulfuric acid (9 mL, con.) in methanol (36 mL). The resultant sky blue colored solution was allowed to warm to room temperature and the reaction was continued until the solution became colorless (1-2 hr). Ethyl acetate (100 mL) and brine (50 mL) were added and the layers were separated. The organic layer was washed with brine (3 x 50 mL) and transferred to a reaction flask. Perchloric acid (2 mL, 1N in EtOAc) and acetic anhydride (11 mL) were added and the solution was refluxed for 0.5-1 hr. The reaction was cooled to room temperature and aqueous sodium

bicarbonate (50 mL) was added cautiously to the stirring mixture. The reaction was continued for 0.5 hour. The layers were separated and the organic phase was washed successively with aqueous bicarbonate (50 mL), water (50 mL), and brine (40 mL), then dried ($MgSO_4$), filtered, and evaporated at reduced pressure. Chromatography on silica gel (20 g, CH_2Cl_2) furnished pure product.

3-Methyl-1(H)-2-benzopyran-1-one (363b). The isocoumarin **363b** was isolated in 84% yield with physical and spectral properties identical to material which was prepared by Method A.

3-Phenyl-1(H)-2-benzopyran-1-one (363c). The isocoumarin **363c** was isolated in 85% yield with physical and spectral properties identical to material which was prepared by Method A.

3-Phenyl-1(H)-2-benzopyran-1-one (363d). The isocoumarin **363d** was isolated in 84% yield with physical and spectral properties identical to material which was prepared by Method A.

3-(4-Methoxyphenyl)-7-methoxy-1(H)-2-benzopyran-1-one (363f). The isocoumarin **363f** was isolated in 79% yield.with physical and spectral properties identical to material which was prepared by Method A.

Method C: (General procedure). Sodium borohydride (0.55 g, 14.6 mmol) was added in small portions to a solution of nitrolactone **359** (4.03 g, 18.2 mmol) dissolved in dimethyl sulfoxide (40 mL) at 10° C and stirred at room temp 1.5 hr. Aqueous sodium hydroxide (1N, 55 mL) was added. The basic solution was added dropwise to a chilled (0 °C) solution of concentrated sulfuric acid (29 mL) in methanol (115 mL). The reaction was stirred 1.5 hr at room temperature until the blue colored solution became colorless. Ethyl acetate (500 mL) was added and the layers were separated. The ethyl acetate solution was washed with brine (4 x 50 mL). The first brine wash was back extracted with ethyl acetate (100 mL) which was then washed with brine (2 x 40 mL) again. The combined organic solution was transferred to a reaction flask. Perchloric acid (5 mL, 1N in EtOAc) and acetic anhydride (20 mL) were added and the reaction was heated at reflux for 1 hr. The solution was cooled to room temperature and aqueous and solid sodium bicarbonate were added until CO_2 evolution ceased. The layers were separated and the organic phase was washed with aqueous bicarbonate (2 x 100 mL), water (70 mL), and brine (50 mL), then dried ($MgSO_4$), filtered, and evaporated at reduced pressure. Chromatography of the residue on silica gel (50 g, CH_2Cl_2) yielded pure product.

3-Methyl-1(H)-2-benzopyran-1-one (363b). The isocoumarin **363b** was isolated in 64% yield with physical and spectral properties identical to material which was prepared by Method A.

3-Ethyl-1(H)-2-benzopyran-1-one (363c). The isocoumarin **363c** was isolated in 85% yield with physical and spectral properties identical to material which was prepared by Method A.

3-Methyl-7-methoxy-1(H)-2-benzopyran-1-one (363e). The isocoumarin **363e** was isolated in 65% yield with physical and spectral properties identical to material which was prepared by Method A.

IV. Phenylnitromethanes

Preparation of Phenylnitromethanes, (General Procedure). A solution of the phenylacetic acid **370** (10.2 mmol) in THF (8 mL) was added to a magnetically stirred solution, chilled (0 °C) solution of LDA prepared from *n*-BuLi (23.5 mmol), diisopropylamine (24.5 mmol), and HMPA (10.2 mmol) under a nitrogen atmosphere. The yellow solution was stirred at room temperature for 1.5 hr then chilled to -60 °C. Addition of methyl nitrate (1.9 mL, 30.6 mmol) to the dianion solution produced a brownish yellow colored solution, which faded to the original yellow color. The reaction was stirred for 1 hr, then acetic acid (1.4 mL) was added and the solution warmed to 0 °C. Hydrochloric acid (12 mL, 4N) was added and CO_2 evolution occurred. Water (20 mL) and ether (20 mL) were added and the layers were separated. The water layer was further extracted with ether (20 mL) and the combined ether extracts were washed successively with water (2 x 20 mL), aqueous bicarbonate (2 x 25 mL), hydrochloric acid

(.01N, 2 x 20 mL), water (2 x 20 mL), and brine (10 mL), then dried (MgSO4), filtered, and evaporated at reduced pressure.

Phenylnitromethane (371a). Distillation of the residue gave a 72% yield of **371a** as an oil with bp 80-83 °C / 2.7 mm (Lit.[141a] bp 90-92 °C / 3mm). ^{1}H-NMR ($CDCl_3$) δ 5.42 (s, 2H, Ar$\underline{C}H_2$), 7.42 (s, 5H, Ar$\underline{H}$); ^{13}C-NMR ($CDCl_3$) δ 79.7, (Ar$\underline{C}H_2NO_2$), 128.8, 129.7 (Ar$\underline{C}$); IR ($CDCl_3$) cm^{-1} 1554, 1375 (NO_2); mass spectrum *m/z* 136 (M^+-1, 1.4), 91 (100).

2-Methoxyphenylnitromethane (371b). Recrystallization (CH_2Cl_2-hexanes) gave an 83% yield of **371b** as white crystals with mp 64-65 °C. ^{1}H-NMR ($CDCl_3$) δ 3.83 (s, 3H, O$\underline{C}H_3$), 5.46 (s, 2H, Ar$\underline{C}H_2$) 6.9-7.5 (m, 4H, Ar$\underline{H}$); ^{13}C-NMR ($CDCl_3$) δ 55.4 (O$\underline{C}H_3$), 74.4 (Ar$\underline{C}H_2NO_2$), 110.8, 118.5, 120.6, 131.5, 131.9, 158.0 (Ar$\underline{C}$); IR ($CDCl_3$) cm^{-1} 1559, 1373 (NO_2); mass spectrum *m/z* 167 (M^+, 8), 131 (32), 121 (100).

3-Methoxyphenylnitromethane (371c). Chromatography of the residue on silica gel (25 g, CH_2Cl_2) gave a 72% yield of **371c** as an oil with bp 82-85 °C / 0.15 mm. ^{1}H-NMR ($CDCl_3$) δ 3.82 (s, 3H, O$\underline{C}H_3$), 5.40 (s, 2H, Ar$\underline{C}H_2$), 6.9-7.5 (m, 4H, Ar$\underline{H}$); ^{13}C-NMR ($CDCl_3$) δ 55.1 (O$\underline{C}H_3$), 79.8(Ar$\underline{C}H_2NO_2$), 115.2, 115.4, 122.0, 129.9, 130.9, 159.8 (Ar$\underline{C}$); IR ($CDCl_3$) cm^{-1} 1555, 1374 (NO_2); mass spectrum *m/z* 167 (M^+, 8), 151 (14), 121 (100).

4-Methoxyphenylnitromethane (371d). Chromatography of the residue on silica gel (25 g, CH_2Cl_2) gave a 77% yield of **371d** as an oil with bp 90-95 °C / 0.15 mm (Lit.[148d] bp 102-103 °C / 0.5mm). ^{1}H-NMR ($CDCl_3$) δ 3.82 (s, 3H, OCH_3), 5.36 (s, 2H, $ArCH_2$), 6.93 (brd d, 2H, ArH), 7.40 (brd d, 2H, ArH); ^{13}C-NMR ($CDCl_3$) δ 55.1 (OCH_3), 79.3($ArCH_2NO_2$), 114.2, 121.8, 131.3, 160.6 (ArC); IR ($CDCl_3$) cm^{-1} 1553, 1373 (NO_2); mass spectrum *m/z* 167 (M^+, 4), 166 (2.2), 121 (100).

3,4-Dimethoxyphenylnitromethane (371e). Chromatography of the residue on silica gel (25 g, CH_2Cl_2) gave a 63% yield of **371e** as a solid with mp 91-92 °C (CH_2Cl_2- hexanes). ^{1}H-NMR ($CDCl_3$) δ 3.90 (s, 6H, OCH_3), 5.37 (s, 2H, $ArCH_2$), 6.8-7.1 (m, 3H, ArH); ^{13}C-NMR ($CDCl_3$) δ 54.4 (OCH_3), 74.1($ArCH_2NO_2$), 109.7, 111.1, 120.7, 121.5, 147.7, 148.9 (ArC); IR ($CDCl_3$) cm^{-1} 1555, 1373 (NO_2); mass spectrum *m/z* 197 (M^+, 1), 151 (100).

2,5-Dimethoxyphenylnitromethane (371f). Chromatography of the residue on silica gel (25 g, CH_2Cl_2) gave a 70% yield of **371f** as an oil with bp 105-107 °C /0.15 mm. ^{1}H-NMR ($CDCl_3$) δ 3.74 (s, 3H, OCH_3), 3.75 (s, 3H, OCH_3), 5.40 (s, 2H, $ArCH_2$), 6.8-7.0 (m, 3H), ArH; ^{13}C-NMR ($CDCl_3$) δ 55.5 (OCH_3), 55.8 (OCH_3), 74.3($ArCH_2NO_2$), 111.8, 116.0, 117.6, 119.0, 152.1, 153.3 (ArC); IR ($CDCl_3$) cm^{-1} 1559, 1372 (NO_2); mass spectrum *m/z* 197 (M^+, 10), 151 (100), 121 (77).

Diisopropylnitramine (372). Methyl nitrate (1.2 mL, 18.2 mmol) was added to a chilled (-60 °C) solution of LDA prepared from *n*-BuLi (7.2 mL, 18.1 mmol) and and diisopropyl amine (2.6 mL, 18.3 mmol) in THF (10 mL) and stirred for 30 min. The reaction solution was warmed to 0 °C, quenched with acetic acid (1.4 mL) and then acidified with hydrochloric acid (4N, 6.5 mL). Water (25 mL) was added and the mixture was extracted with ether (2 x 25 mL). The organic layer was washed with sodium bicarbonate (2 x 15 mL), water (2 x 10 mL), and brine (10 mL), then dried ($MgSO_4$), filtered, and evaporated at reduced pressure. The residue was sublimed (80 °C / 0.5 mm) to give a white solid. ^{1}H-NMR ($CDCl_3$) δ 1.35 (d, 12H, J = 6.6 Hz, $CHC\underline{H}_3$), 4.2-4.6 (m, 2H, $C\underline{H}CH_3$); ^{13}C-NMR ($CDCl_3$) δ 19.4 ($CH(\underline{C}H_3)_2$), 50.6 ($\underline{C}H(CH_3)$; IR (KBr) cm^{-1} 2982, 2939 (aliphatic C-H), 1504, 1301 ($N\text{-}NO_2$).

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