AN ABSTRACT OF THE THESIS OF

Ernest G. Nolen Jr. for the degree of Doctor of Philosophy in Chemistry presented on December 10, 1984.

Title: Approaches toward the Asymmetric Synthesis of Pillaromycin A.

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James D. White

Pillaromycin A, an antibiotic natural product, displays antitumor activity with relatively low cardiotoxicity compared to the structurally similar anthracyclines. In this study, asymmetric approaches toward the synthesis of the tetracyclic aglycone are presented.

A convergent route was developed around a C ring annulation strategy, whereby the anion of ethyl 6-methoxy-2-methylbenzoate (34) was condensed with an appropriate β-alkoxy-α,β-unsaturated ketone of the AB ring synthon 88A.

An approach to an asymmetric AB ring synthon was initiated from D-glucal 49 and carried through the critical intramolecular Diels-Alder reaction via the (7S,8R)-7-acryloxy-8-acetoxy-2-t-butyldimethylsiloxy-3,5-nonadiene (59). Three Diels-Alder products were obtained in a ratio of 2.5:2.5:1, in 85% yield. The two major isomers were believed to each possess the opposite absolute configuration about the allylic ring fusion C(4a) to that of pillaromycinone.

A parallel sequence to the AB ring system of pillaromycinone was achieved from L-rhamnal. Glycolization and protection of the

Diels-Alder adducts afforded isomers 81 and 83 confirming the correct absolute configuration at C(4a) in the major Diels-Alder products. Conversion to the B ring 1,3-dione, followed by O-alkylation, afforded the asymmetric AB ring synthon 88A.

A convergent assembly of the tetracyclic nucleus of pillaromycinone was accomplished via the condensation of 34 and 88A. Concomitant C ring annulation and aromatization yielded 32% of the (2R,3S,4R,4aS)-3,4-dihydroxy-(1,2,3,4,4a,12a)-hexahydro-11-hydroxy-10-methoxy-2-(1-t-butyldimethylsiloxyethyl)-12(5H)-naphthacenone ketal (89).

Approaches toward the Asymmetric Synthesis of Pillaromycin A.

by

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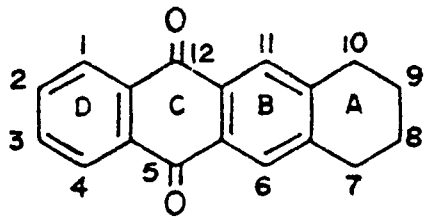
APPROACHES TOWARD THE ASYMMETRIC SYNTHESIS OF PILLAROMYCIN A

I. INTRODUCTION

The anthracycline antibiotics possess potent antitumor activity, thereby making them the target of a vast amount of research. Chemical and biochemical studies have provided an array of anthracyclines for evaluation of their structure-activity relationship. This search for structure-activity correlations aspires to improve their clinical use in cancer chemotherapy.[1-3]

An anthracycline, according to the National Cancer Institute, is defined as a 7,8,9,10-tetrahydro-5,12-naphthacenequinone 1 connected to at least one sugar moiety. The numbering system and letter designation of the rings in the aglycone are shown in 1. It should be noted that 10% of the anthracyclines vary from this definition by possessing unique structural differences.[4]



1

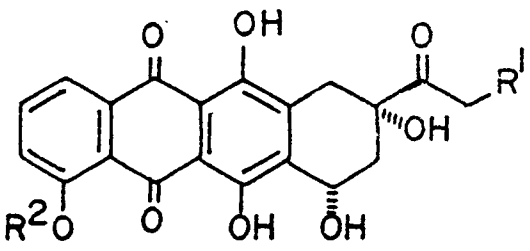
The first anthracycline, β-rhodomycin, was isolated from Streptomyces purpurascene by Brockmann and Bauer in 1950.[5] In culture,

β-rhodomycin exhibited potent antibacterial activity, although it was a highly toxic compound. In 1959, the cinerubins were isolated and were shown to be active against gram-positive bacteria and to inhibit various murine sarcomas and carcinomas.[6] Unfortunately, their high toxicity prevented their development as antitumor agents. Not until 1963 was the first antitumor anthracycline with a favorable therapeutic index discovered. This substance was named daunomycin, also referred to as rubidomycin and daunorubicin.[7] Daunomycin exhibited even higher antineoplastic activity than the known antitumor antibiotics mitomycin C and actinomycin C.

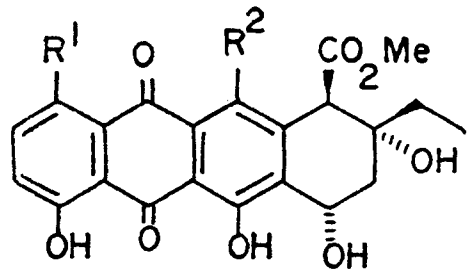
Subsequent research led to the isolation and characterization of a plethora of anthracyclines, a few of which are shown in figure 1 as their aglycones.

Anthracyclinones typically are highly crystalline compounds that are soluble in most organic solvents and relatively insoluble in water and petroleum ether. The aglycones show substantial dextrorotation of polarized light at the sodium D wavelength. Circular dichroism curves of anthracyclinones are characteristic in the 270-390 nm region, where they typically show a similar S shape due to a positive Cotton effect. Also, the hydroxyanthraquinone chromophore displays a characteristic visible color, varying from red to yellow.

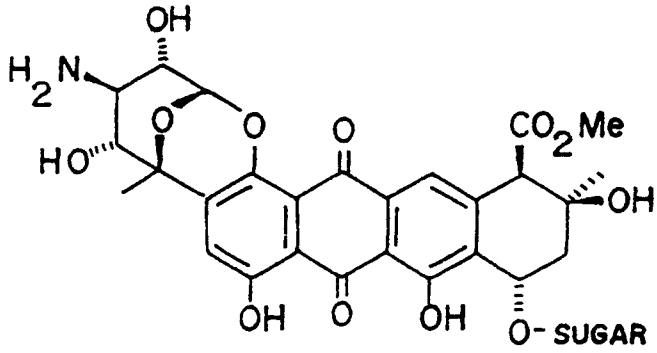
The anthracycline most widely known for its antitumor action is adriamycin, also named doxorubicin. Isolated from a strain of Streptomyces peucetius in 1969,[8] this 14-hydroxy analog of daunomycin has become one of the most useful cancer chemotherapeutic agents to date. It is active against a broad range of solid tumors in man. As a class



R^1=H; R^2=Me, daunomycinone
R^1=OH; R^2=Me, adriamycinone
R^1=H; R^2=H, carminomycinone



R^1=H; R^2=H, aklavinone
R^1=H; R^2=OH, ε-rhodomycinone
R^1=OH; R^2=H, ε-pyrromycinone



nogalamycin

Figure 1. Various Anthracyclines.

solid tumors are most resistant to chemotherapy and medical progress in their treatment has been limited. Carter[9] has reported that adriamycin has significant activity in nine of nineteen human tumors on which treatment statistics are complete. Table I provides a summary of adriamycin's activity against some human tumors. Patients were administered 60-75 mg/m^2 intravenously every three weeks. Responses were recorded after approximately two months. A response was defined as a greater than 50% reduction in tumor mass, except in the case of acute leukemia.

It should be noted that the results in Table I were based upon single-drug treatment. Many of the most effective treatment regimens

Table I. Response of Some Human Tumors to Adriamycin

Type of Tumor	Reduction in Tumor Mass
Breast cancer	36%
Sarcomas	26%
Lung cancer	19%
Malignant lymphomas	41%
Acute leukemia	24%

for cancer are based on combinations of drugs. Consequently, adriamycin, when coupled with other known antitumor drugs, shows a marked increase in effectiveness.

As is common with most antitumor drugs, adriamycin induces toxic side effects. Table II summarizes the incidence of the most common reactions. These effects are generally reversible except for myocardiopathy. The cardiotoxic effects are dose-related, and a cumulative dose of <500 mg/m^2 yields a low incidence of myocardiopathy. A retrospective analysis has shown a 33% rate of myocardiopathy as the dosage is increased. Myocardiopathy is most often manifested as a rapidly progressing syndrome of congestive heart failure. This limits the use of adriamycin at the present time.[10,11]

Both adriamycin and daunomycin have been shown to have similar mechanisms of action at the molecular level. Both antibiotics rapidly inhibit nucleic acid synthesis *in vitro* and *in vivo*. Biophysical and biochemical studies have shown evidence for anthracycline intercalation of double helical DNA. Complexed DNA shows changes

Table II. Incidence of Adverse Reaction to Adriamycin.

Reaction	Number of Patients Exhibiting Reaction
Leukopenia	60-75%
Alopecia	80-100%
Cardiac Irregularities	
EKG	6-30%
Myocardiopathy	0.4-1.2%
	33%*
Nausea	50%
Stomatitis	80%

*These received >500 mg/m^2.

in viscosity, thermal denaturation-renaturation, and optical activity. The drugs show changes in visible absorption, ultraviolet absorption, fluorescent emission, and polargraphic behavior upon complexation with DNA. These changes and the ability of DNA to sediment with the antibiotic correlate well with those of known intercalators, such as the actinomycins. More direct evidence for intercalative binding has been revealed by x-ray diffraction studies on the daunomycin-DNA complex. The resulting model, figure 2, reveals the aglycone portion intercalated between adjacent base pairs with the glycoside lying in the major groove of the helix. The amino sugar interacts

strongly with the second DNA phosphate removed from the intercalation site. An additional element of stabilization arises from hydrogen bonding of an adjacent DNA phosphate with an A ring hydroxyl. These interactions cause an unwinding of the double helix by 12°, resulting in a longer and stiffened structure. The net effect can be a misrepresentation of the genetic expression, with inhibition of DNA polymerase and DNA-dependent RNA polymerase.[12-15].

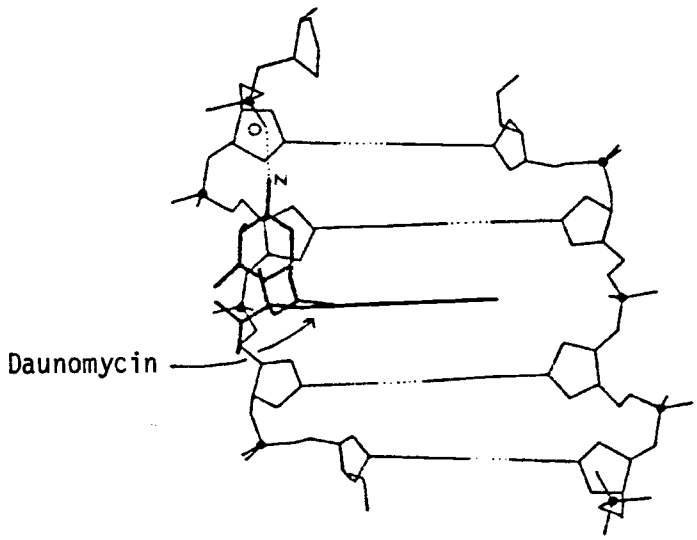


Figure 2. Daunomycin-DNA complex.

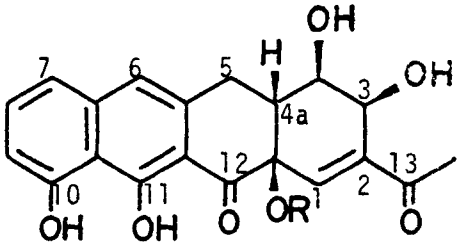
Although anthracycline intercalation and its physical consequences to DNA have been clearly described, they explain only a part of the overall picture. Both adriamycin and daunomycin bind to all

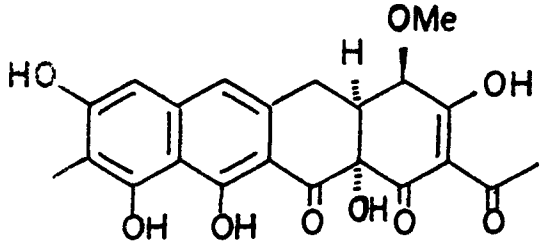
forms of DNA and presumably in all cells into which the agents penetrate, so it is difficult to see how intercalation contributes to cytotoxic specificity without involving several mechanisms. Further work has hinted at specific drug effects attributable to the plasma membrane, which is the first cellular encounter for the drug and therefore is the first determinant of selectivity. Also, the drug levels or rates of depletion from the surrounding medium have been shown to be important determinants of cytotoxicity. One important condition may be the degree of aeration; this may, in turn, determine the formation of oxidized or reduced drug forms. Reduction of the quinone moiety triggers biological activation, which may account for some selectivity under the relatively anaerobic conditions sustained by some cells in solid tumors.[16,17]

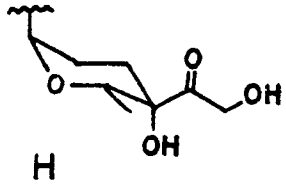
The relationship between chemical structure and biological activity is of considerable importance in the design or derivatization of new drugs. The task of designing anthracyclines with greater antitumor potency or lower cardiotoxicity can be simplified if a consistent set of relationships can be established. A broad range of anthracyclines has been tested; in fact over five hundred derivatives of daunomycin have been systematically examined. One of the most potent analogs found to date is the N-trifluoroacetylglycoside of adriamycin but, unfortunately, toxicity remains high. A less potent anticancer agent, carminomycin, with relatively low cardiotoxicity is being developed for clinical use in the Soviet Union. The aclacinomycin group, exemplified by aklavinone linked with a trisaccharide, has similar properties and is currently enjoying

substantial success in preclinical trials.[18,19] Pillaromycin A (2) has also been shown to be an effective antineoplastic agent, while retaining a relatively low cardiotoxicity.[20,21]

Pillaromycin A (2) was obtained from Streptomyces flavovirens in 1964. An x-ray analysis[22] of the pillarone monobromoacetate (described later) established the absolute configuration of the aglycone in 1970. Its structure differs from most anthracyclines by the absence of the C ring quinone and the lack of aromatization in the B ring. The highly functionalized A ring possesses an all-cis triol moiety with one tertiary and two secondary hydroxyls. The tertiary alcohol, located at the AB ring fusion, provides the glycoside linkage to the novel sugar, pillarose.[23,24] A clear resemblance of pillaromycinone (3) to chromocycline (4) is noteworthy.[3]





2; R = 

3; R = H

4

The anthracycline antibiotics arise biogenetically from a decaketide involving one propionate and nine acetate units.[25,26] Blocked

mutants derived from Streptomyces were used to examine the biosynthetic pathway shown in figure 3. Akiavinone (AKN) has been revealed as a main biogenetic source for several aglycones. Microbial oxidation at C(1) supplied ε-pyrromycinone (ε-PMN), while modification of the inhibiting microbe furnished the 11-hydroxyderivative, ε-rhodomycinone (ε-RMN). Removal of the C(10) carboxymethyl group led to daunomycinone (DMN), which was further elaborated to adriamycinone (AMN).

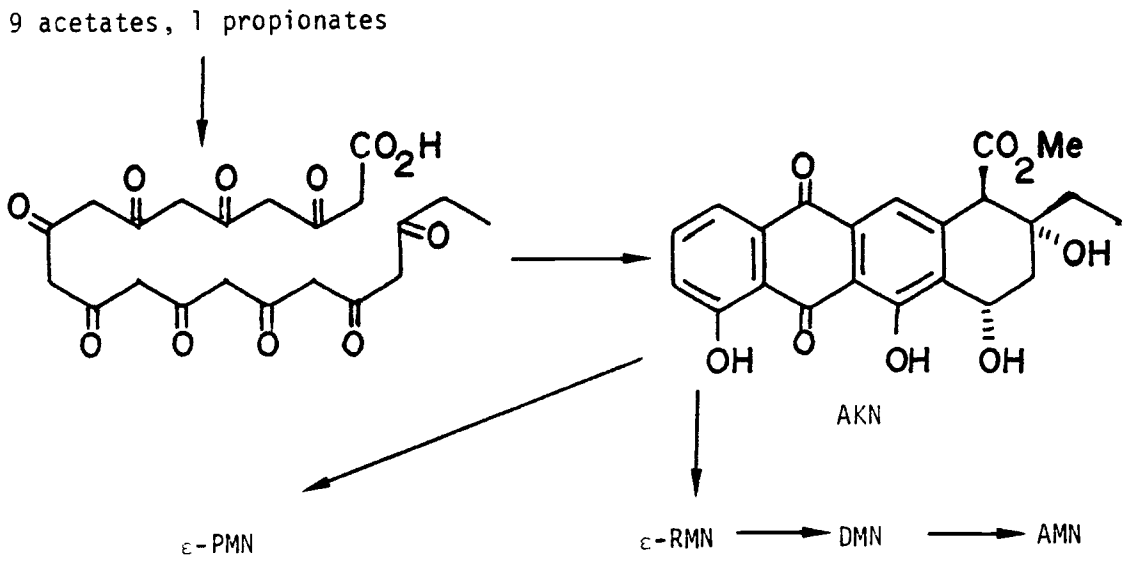


Figure 3. Biosynthetic Pathway.

From a synthetic viewpoint, polyketide cyclization is an unreasonable route to mimic, due to the total lack of regiocontrol which can be expected. However, many total syntheses of the anthra-

cyclinones have been achieved with high regio and stereoselectivity.[27-40] A representative sample of some key work in this domain is outlined in figure 4. However, in spite of the great amount of attention anthracyclines have received, none of the existing syntheses can be readily adapted to the unique pillaromycinone structure (figure 4, page 11).

Asai et al., who isolated pillaromycin, have also made several derivatives of the antibiotic.[41,42] Pillaromycin has been hydrolyzed to the aglycone. Pillaromycinone (3) has been protected as the tetraacetate 5 or pentaacetate 6. Methylation of the two phenolic oxygens has also been accomplished. The cis glycol of the A ring has been transformed to the isopropylidene derivative 8. Finally, the A ring unsaturation has been reduced to supply the saturated ketone 9 or the internally ketalized structure, pillarone (10). The lone secondary alcohol of pillarone has been removed via conversion to the sulfide, followed by Raney nickel reduction. Selective monobromoacetate formation gave the pillarone derivative 11 examined in the aforementioned crystallographic work.

To date, only one synthetic route directed toward pillaromycinone has been reported, that by Trost in 1983.[43] His strategy began with a CD ring synthon and connected rings B and A by sequential Diels-Alder reactions. The Trost route originated from a regiocontrolled cycloaddition involving juglone (12) and 1-acetoxybutadiene. Upon reduction and protection of the quinone, the α,β-unsaturated ketone 14 was generated. A second, regiospecific Diels-Alder reaction was accomplished with 2-acetoxy-3-(p-anisylthio)butadiene to afford

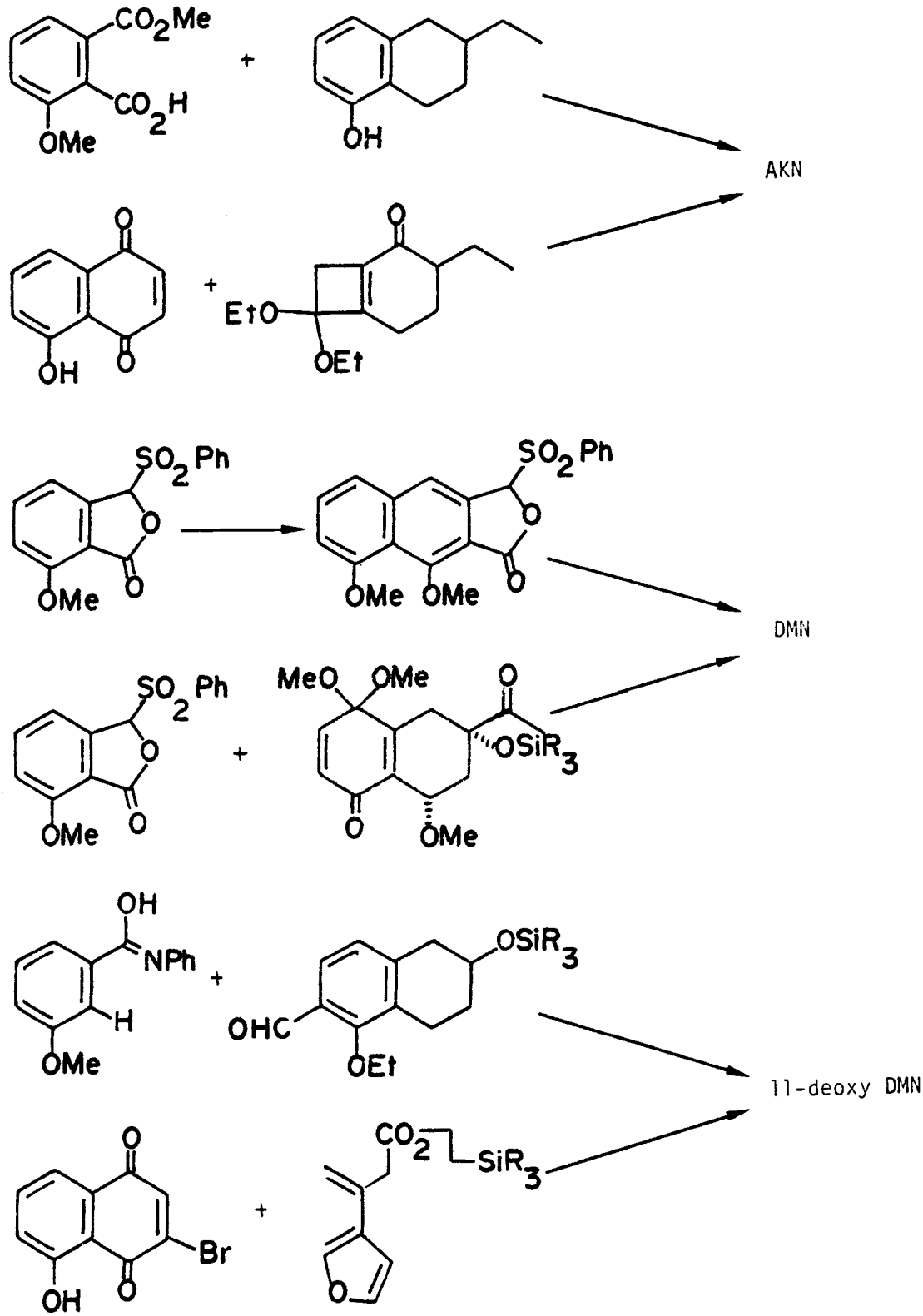


Figure 4. Anthracycline Syntheses.

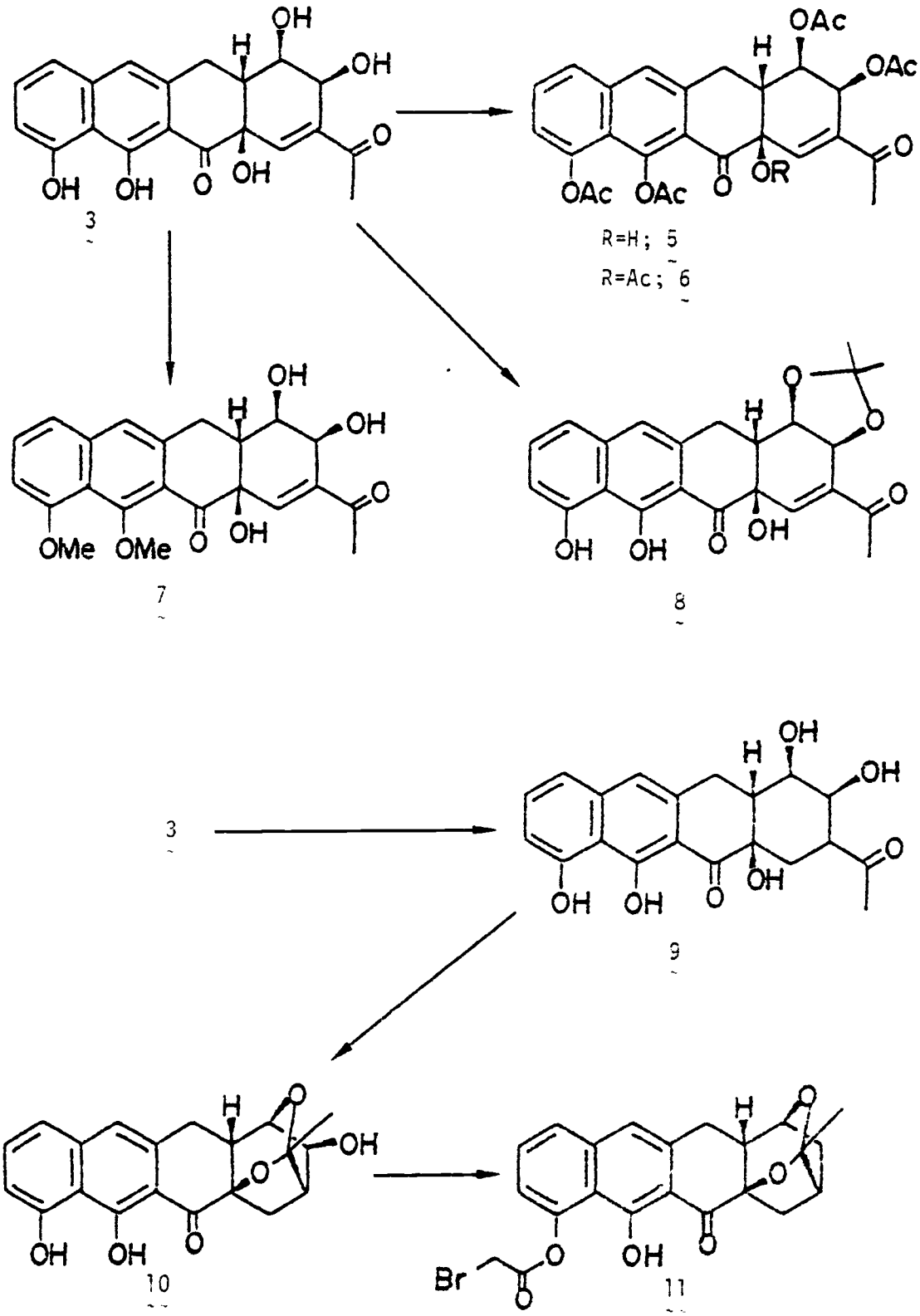


Figure 4 continued.

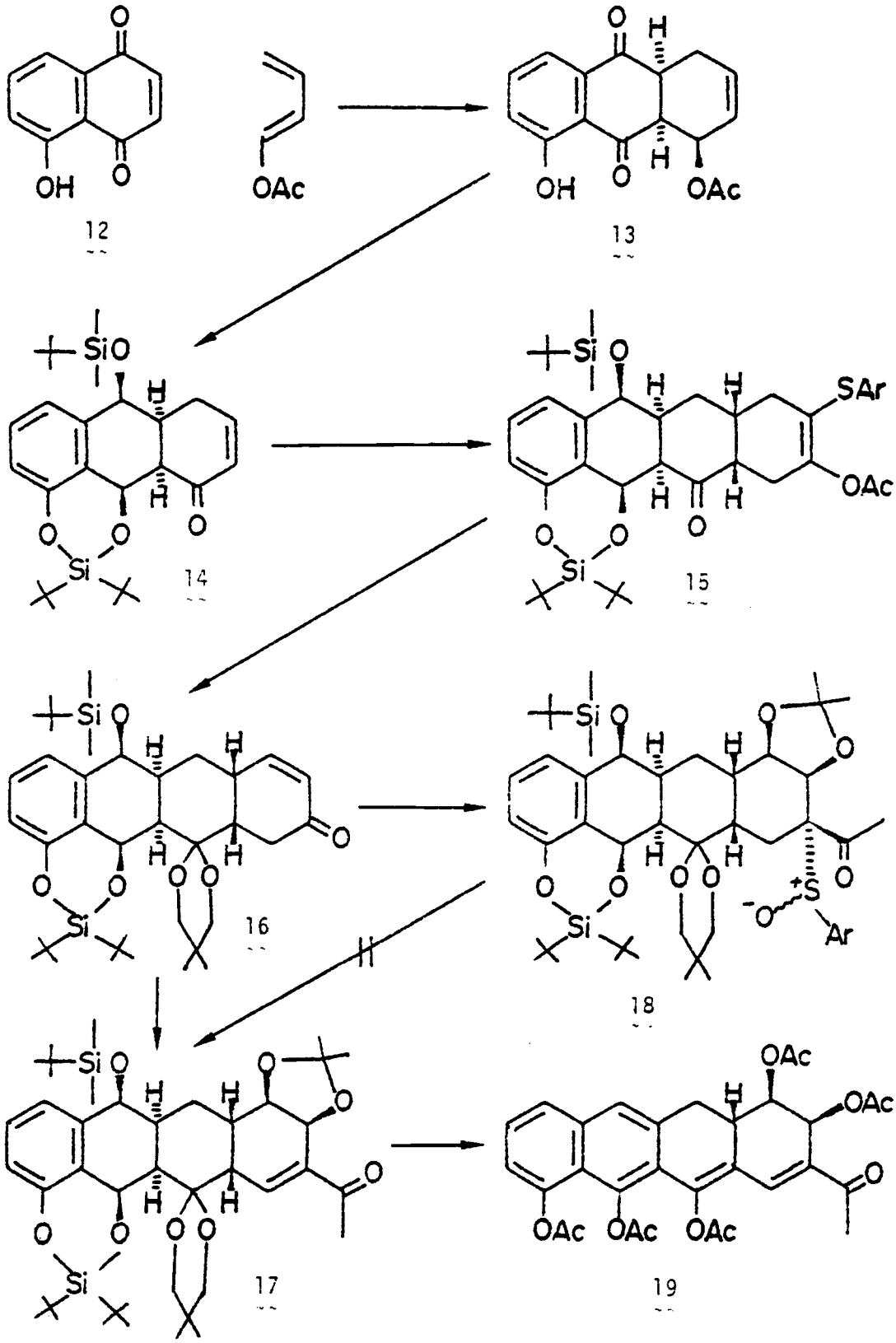


Figure 4 continued

the tetracyclic intermediate 15, which was subsequently transformed to the A ring enone 16. At this point, more complete elaboration of the A ring was achieved by glycolization and addition of the acetyl unit. It should be noted that the C(1-2) unsaturation could not be selectively introduced via intermediates such as the α-sulfenyl ketone 18. Finally, careful deprotection, aromatization, and acetylation provided the pentaacetate of 12a-deoxypillaromycinone (19).

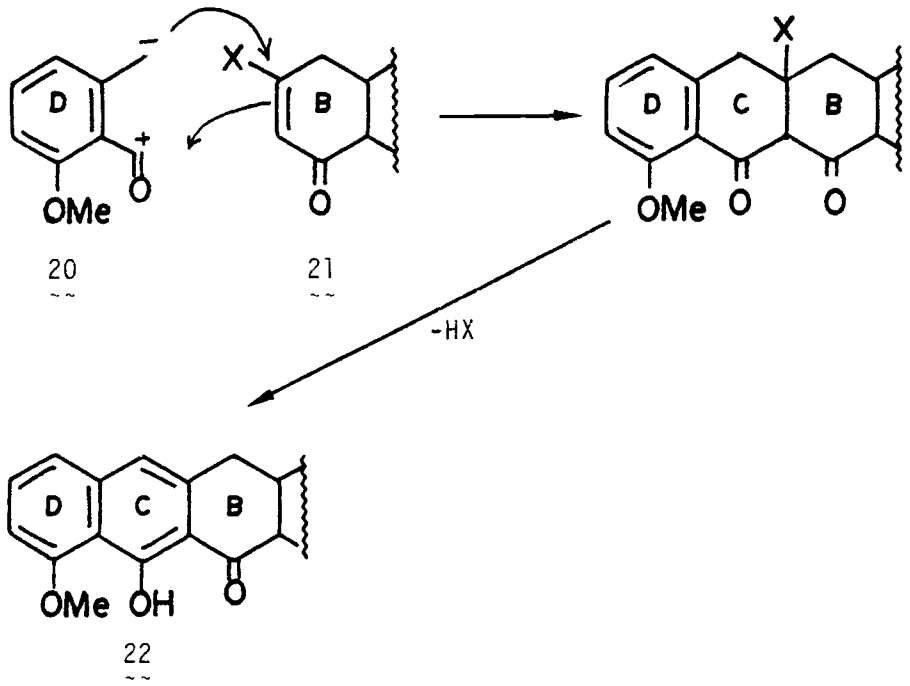


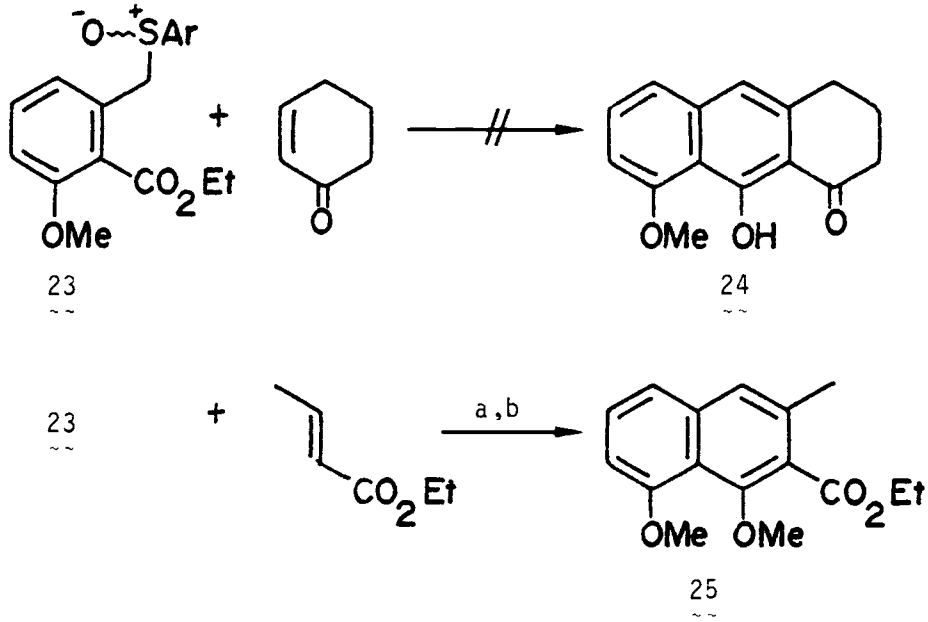
Figure 5. General Ring Foramtion Strategy.

An alternative report describing our approach towards pillaromycinone follows. Our strategy for entry into the pillaromycinone

ring system involved a condensation of the D ring with an AB ring synthon, thereby establishing the C ring. Successful C ring annulation required formation of an o-toluate anion 20, a Michael reaction of this anion with a cyclohexenone derivative 21, an intramolecular cyclization of the resulting enolate with the benzoate ester, and finally elimination to generate the aromaticity of 22. Figure 5 illustrates this plan. It was intended that an appropriate AB ring synthon would possess all remaining carbons, thus resulting in a highly convergent synthesis, and that the four contiguous chiral centers would be set in place prior to coupling of the two subunits 20 and 21.

II. C RING STRATEGY

A convergent approach involving an annulation process was investigated for connection of two pillaromycinone subunits. Initial studies were directed toward some model coupling reactions along the lines described by Hauser.[44] The sulfoxide 23 was generated from readily available ethyl 2-methoxy-6-methylbenzoate.[45] The sulfoxide substituent enhances the stability of the benzylic anion and also serves as the functional grouping eliminated for aromatization. Efforts to react the sulfoxide-stabilized anion with cyclohexenone

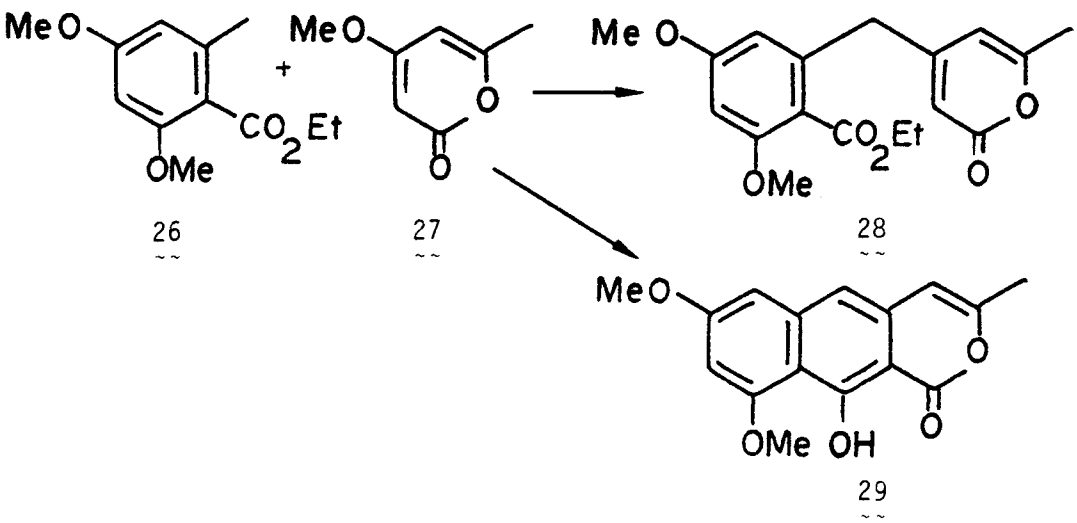


23 24

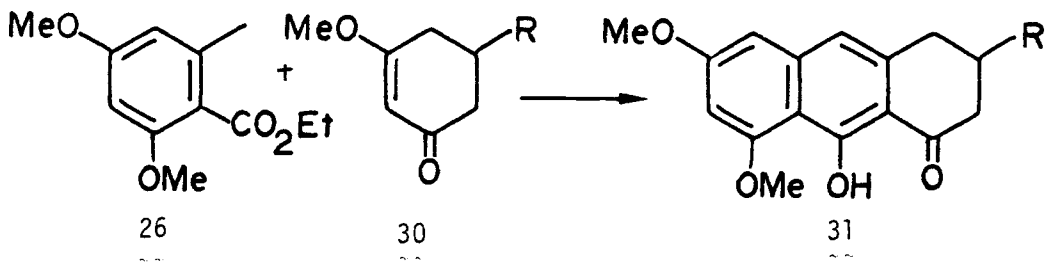
23 + → 25

a.LDA, THF; b.Me_2SO_4, K_2CO_3, acetone

failed to yield 24, giving only recovered aromatic material and polymerized cyclohexenone. The anion of 23 did condense with ethyl crotonate however, to supply the naphthoate 25 after methylation. The naphthylic anion from 25 proved to be inert toward further Michael reaction, presumably due to its extended conjugation.



26 27 28 29

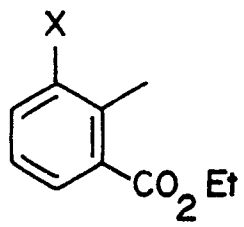


26 30 31

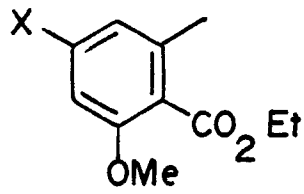
Weinreb and Staunton have investigated an alternative route to polycyclic aromatic structures, in which the anion of orsellinate 26 was condensed with vinylogous esters.[46,47] Staunton generated

the orsellinate anion by employing 1.95 equivalents of lithium diisopropylamide, and successfully condensed it with the triacetic lactone methyl ether 27 at -78°C to obtain the 4-substituted α-pyrone 28. If the reaction was allowed to warm briefly to room temperature before acidification, the fluorescent naphthopyrone 29 could be isolated in 75% yield. Weinreb, in his approach toward the aureolic acids, condensed the β-methoxy enone 30 with orsellinate to give the tricyclic ketone 31 in 75% yield. These are excellent yields compared to those obtained previously by these two groups.[48,49]

It has been noted that the anion 32 and its ortho substituted counterpart 33 dimerize rapidly and cannot be used synthetically, even though the orsellinate anion 26 is stable at low temperatures.[44,50] Staunton states that the stabilization of orsellinate anion is due to the ortho methoxy substituent which sterically hinders the carbonyl from nucleophilic attack.[51] Another stabilizing factor may be electron donation by the ortho and para methoxy groups toward the carbonyl. In addition, these methoxy substituents are meta to the negative charge and consequently, stabilize the anion by an inductive effect.



X=H; 32
X=OMe; 33



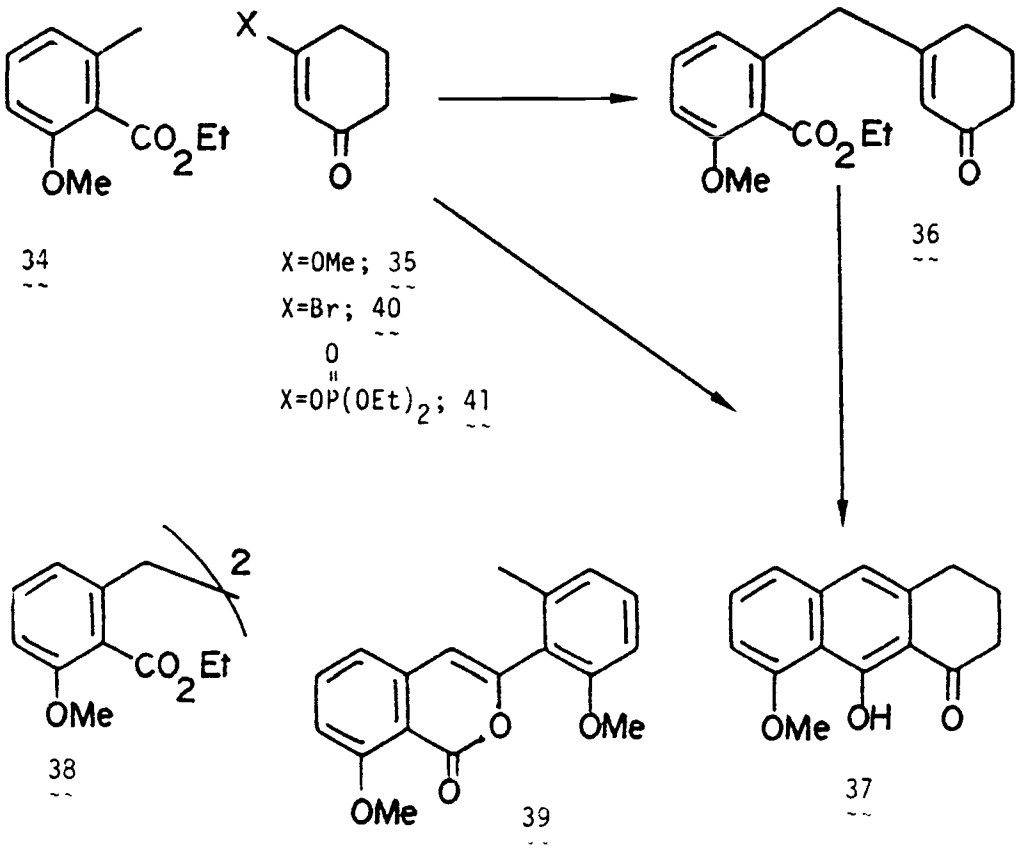
X=H; 34
X=OMe; 26

The toluate species 34 required for entry to the pillaromycinone nucleus has only one of these methoxy substituents, and is therefore destabilized relative to orsellinate, but is more stable than 33.

In the present study, the reaction of β-methoxy cyclohexenones 35 with the anion of 34, generated with two equivalents of lithium diisopropylamide at -78°C, were examined. Quenching the reaction at -78°C furnished 36 but, when the reaction was permitted to warm to room temperature before quenching, a mixture of 36 (35%) and anthracenone 37 (28%), was obtained, along with some toluate dimer 38 and self-condensation product 39. The cyclohexenone 36 could be converted to the tricyclic species 37 by treatment with sodium ethoxide in ethanol, but in only 24% yield.

Attempts to enhance the reactivity of the cyclohexenone 35 toward 34 were explored by varying the β-stubstituent. 3-Bromo-2-cyclohexen-1-one (40)[52] and the enol phosphate 41 of 1,3-cyclohexanedione[53] were each condensed with the anion of 34 under the previously described reaction conditions. However, these reactions were judged synthetically useless due to extensive polymerization.

A modified route to 37 was investigated using 2-phenylselenylcyclohexenone (42). It was expected that incorporation of the selenyl group would enhance the Michael reaction with 34 by stabilizing the resulting enolate. This substituent would also allow for eventual aromatization through selenoxide elimination. The phenylselenylenone 42 was obtained directly from cyclohexenone, phenylselenyl chloride,



and pyridine, as described by Liotta.[54] The condensation of 42 with the toluate anion 34 gave the expected product 43 of 1,4-addition but, unfortunately, the increased stability of the resulting enolate rendered it inert to intramolecular, nucleophilic attack at the carboxylate function.

The yields of 37 using toluate 34 and β-alkoxyenones are modest, yet essentially three reactions have taken place: Michael addition,

34 42 43

intramolecular condensation, and elimination to generate a naphthalene. With this annulation accomplished, the next phase of the study focused on an asymmetric synthesis of an AB ring synthon. The coupling of 34 with this segment would then be employed at a later stage of the synthesis to complete the tetracyclic nucleus of pillaromycinone.

III. SYNTHESIS OF THE AB RING SYNTHON

A chiral synthesis of pillaromycinone (3) requires a component representing the A and B rings with the correct absolute configuration. The retrosynthetic plan outlined in figure 6 designates the decalin derivative 44 as the target structure for this segment. The AB ring system of 44 embodies all four chiral centers present in 3, while the β-alkoxyenone required for coupling to 34 is located in ring B. Incorporation of the tertiary hydroxyl at the AB fusion and the C(1-2) unsaturation was envisioned for the last stages of the synthesis.

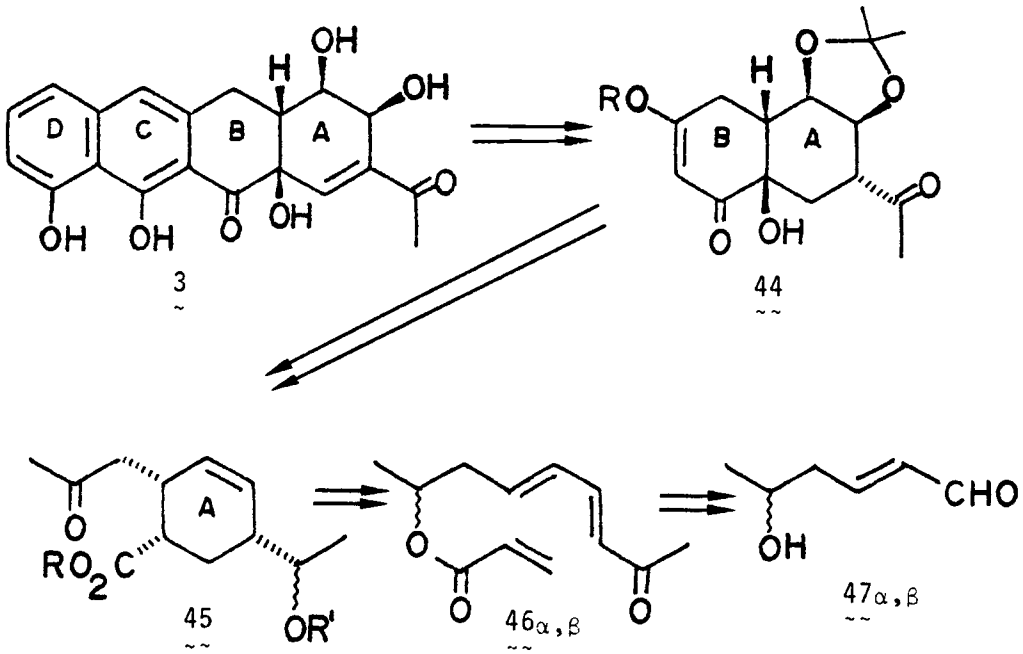
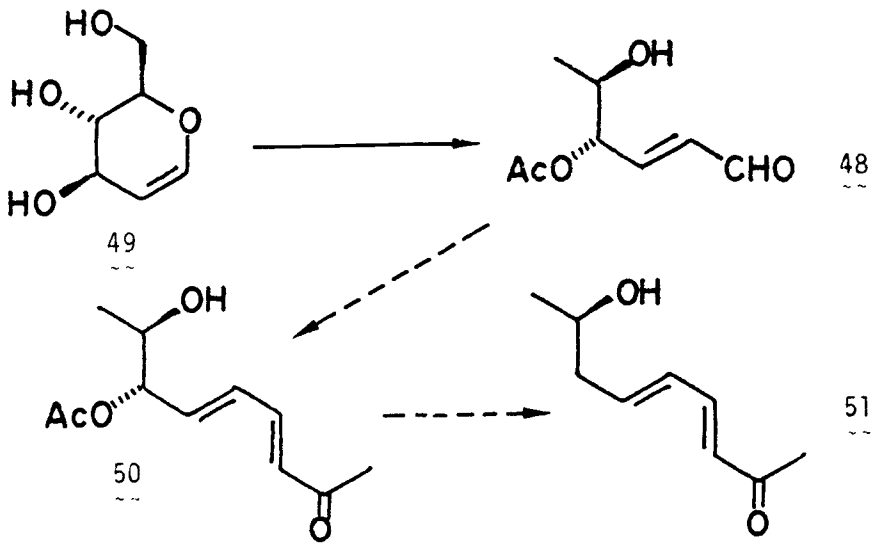


Figure 6. Retrosynthetic Plan.

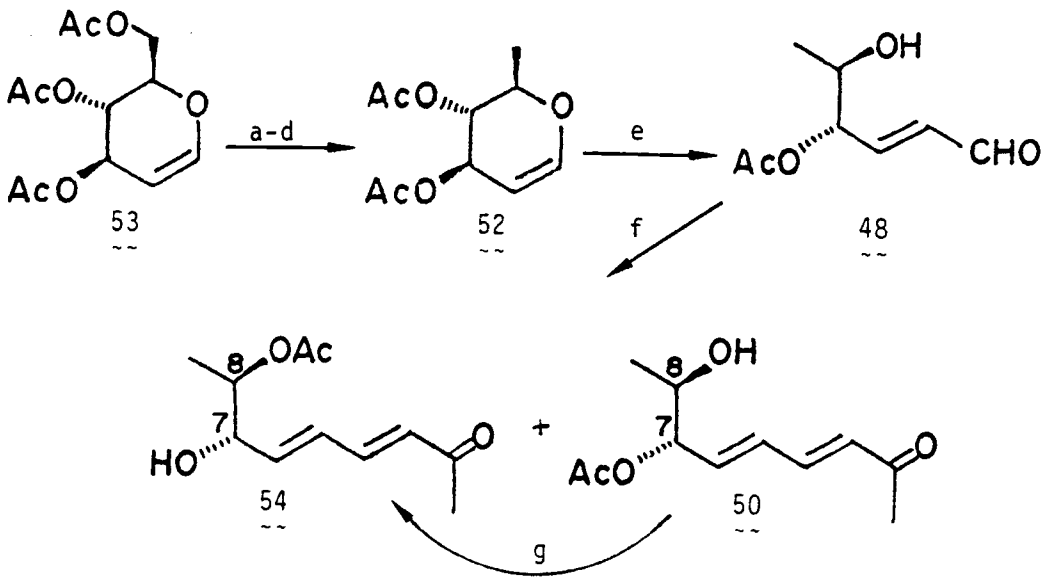
The cis β glycol of 44 would be available from the alkene 45 providing both of the allylic chains are α, as drawn, and formation of the B ring was projected via intramolecular acylation of 45. Since the acetyl appendage required for 44 could interfere with this annulation, its protection in the form of the reduced ether, as shown in 45, was judged to be advisable. For the construction of 45, an intramolecular Diels-Alder reaction appeared to be ideal, as such reactions are known to be remarkably efficient for the simultaneous assembly of several stereocenters. Trienoate 46, where α and β refer to the bond of undefined stereochemistry, was chosen as the precursor of 45. The nonadienone portion of 46 can be derived conceptually from a Wittig olefination of the hexenal 47.

A. AN APPROACH FROM D-GLUCAL

The hexenal 47α can be obtained in seven steps[55] from resolved 2-hydroxybutyric acid.[56] The hexenal can also be related to a deoxygenated sugar, in which the C(5) hydroxyl is still intact. In fact, a synthesis of 47α has been reported from D-glucose in eleven steps.[57] Our strategy, however, was to begin with 5-hydroxy-4-acetoxy-2-hexen-1-al (48), which is available from D-glucal (49) in four steps. It was supposed that, after Wittig olefination of 48, the allylic acetate of the dienone 50 could be reductively eliminated to furnish 51.



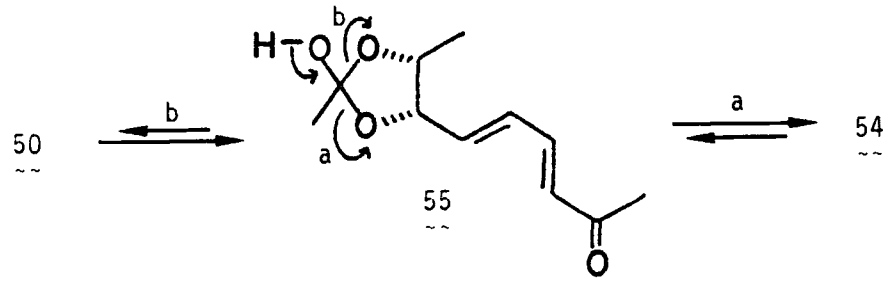
The 6-deoxyglucal 52 was obtained in an overall 50% yield from the commercially available triacetoxyglucal 53 by the route shown. A Perlin transformation of 52 gave rise to the E-hexenal 48 (95%), contaminated with ca. 5% of its 5-acetoxy-4-hydroxy isomer.[58] Wittig olefination using the triphenylphosphineacetylmethylene supplied an 85-95% yield of two isomeric E,E,-dienones, in a ratio of 3.5:1. The NMR spectrum of the major isomer, which displayed a doublet of quartets for the C(8) proton at δ 4.96, corresponded with structure 54. On the other hand, the C(7) proton resonance of 50 revealed a doublet of doublets at δ 5.24. The rearrangement product 54 was thought to be due to a trace of potassium carbonate in the ylide. In support of this conjecture, thorough purification of the ylide and subsequent reaction with 48 afforded a ratio of E,E-dienones which was reversed



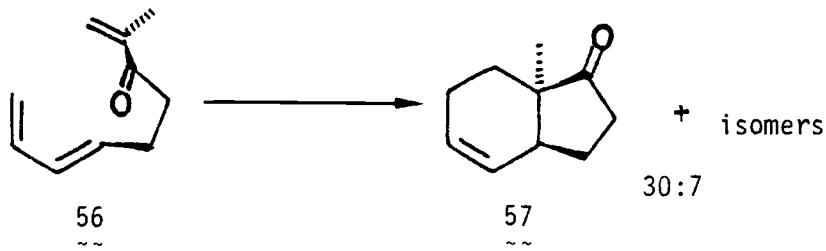
a.NaOMe, MeOH; b.TsCl, py; Ac_2O; c.NaI; d.n-Bu_3SnH; e. $HgSO_4$, H_2SO_4, dioxane, acetone; f.$Ph_3P{=}CH{-}C(O)CH_3$, benzene; g.NEt_3

(2:1) in favor of the unrearranged 7-acetoxy-8-hydroxydienone 50. The pure isomer 50 gave a 3:1 mixture of 54:50 upon treatment with triethylamine. The acetate migration, which accompanies the Wittig reaction of 48, is thought to proceed through the tetrahedral intermediate 55. Basic conditions enhance the formation of 55 by increasing the nucleophilicity of the alcohol. Collapse of the orthoester via disconnection of bond b returns isomer 50; however, cleavage of bond a affords the sterically favored isomer 54.

Fortunately, this unanticipated acetate migration could be used to our advantage. With the C(7) hydroxyl now available for linkage



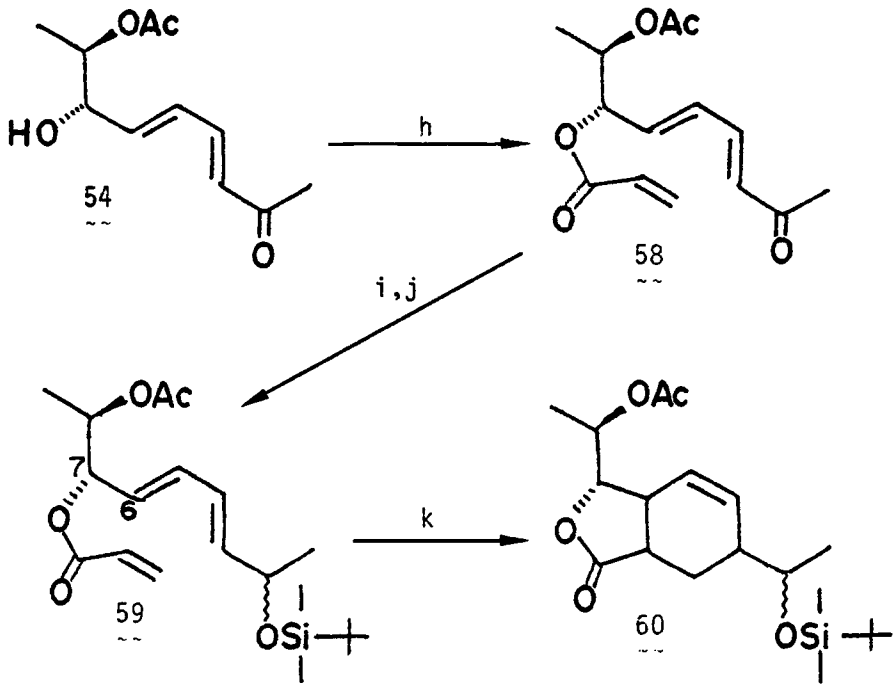
to the dienophile, the chiral center from which subsequent stereochemistry is directed would be closer to the diene moiety and thus better situated for chirality transfer in the crucial, intramolecular Diels-Alder reaction. Also, cycloaddition would result in a fused γ-lactone rather than a δ-lactone. Sutherland has shown, in an achiral example 56, that a dienophile bearing an activating carbonyl in the linking chain yields predominantly the cis fused hydrindanone 57.[59] Cis fusion, which is a result of an endo mode of addition, contrasts here with many intramolecular Diels-Alder reactions of terminally activated dienophiles, which proceed via an exo mode.[60]



Investigation of the intramolecular cycloaddition employing the sugar-derived diene 54 seemed worthwhile, particularly since there are very few studies in which chirality is transferred from a site in the connecting chain.[61,62]

Toward this end, 54 was esterified with acryloyl chloride to furnish in high yield the trienoate 58. However, attempted cycloaddition of 58 was unsuccessful, presumably due to the deactivation of the diene. To remove the deactivating influence of the ketone on the diene, a careful reduction with sodium borohydride in the presence of cerium trichloride (to prevent 1,4-hydride addition)[63] was effected. The resulting alcohol was protected as its t-butyldimethylsilylether 59. In contrast to 58, this substance did undergo cycloaddition when heated in toluene at ca. 210°C in a stainless steel high pressure reactor (Parr type). Elevated temperatures were necessary to overcome the dipole-dipole interactions in the ester linkage.[64] Standard precautions were taken, such as degassing the solution, silylation of the container, and addition of a radical inhibitor.

An analysis of the Diels-Alder reaction of 59 revealed subtle but significant differences in the four principal pathways, figure 7. Transition states with the acrylate positioned above the diene are referred to as β, while those with the acrylate below the diene are termed α. Endo and exo describe the orientation of the ester chain linking the diene with dienophile. The critical C(6-7) bond is the primary locus of the nonbonded interactions between the sterically demanding acetoxyethyl (R) group and the diene. The two β transition states maintain relatively few nonbonded interactions. In particular,



h.CH_2=CH-C(O)Cl, diisopropylethylamine, CH_2Cl_2; i.$NaBH_4$, $CeCl_3$, MeOH; j.TBDMSi-triflate, 2,6-lutidine, CH_2Cl_2; k.210°C

the β-endo conformation places the acetoxyethyl group anti to the diene moiety. In contrast, the two α transition states are sterically encumbered. The α-exo geometry is especially unfavorable, since it involves an eclipsing interaction of the acetoxyethyl substituent with the diene. Based on this analysis, the Diels-Alder reaction of 59 was predicted to yield a preponderance of isomers with absolute stereochemistry at the allylic ring fusion opposite to that of C(4a) of pillaromycinone.

Examination of the mixture resulting from intramolecular Diels-Alder reaction of 59 revealed three products, separable by flash

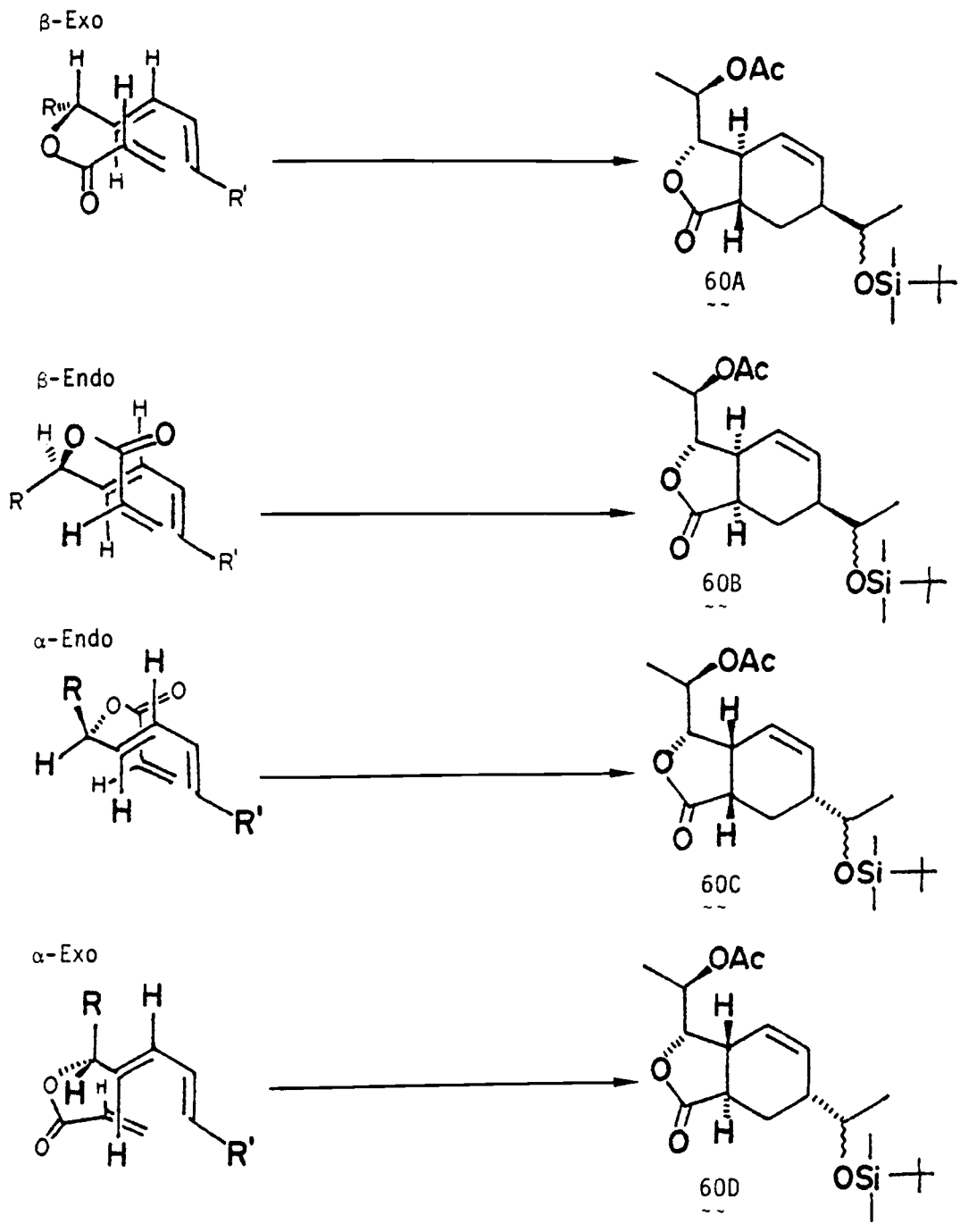
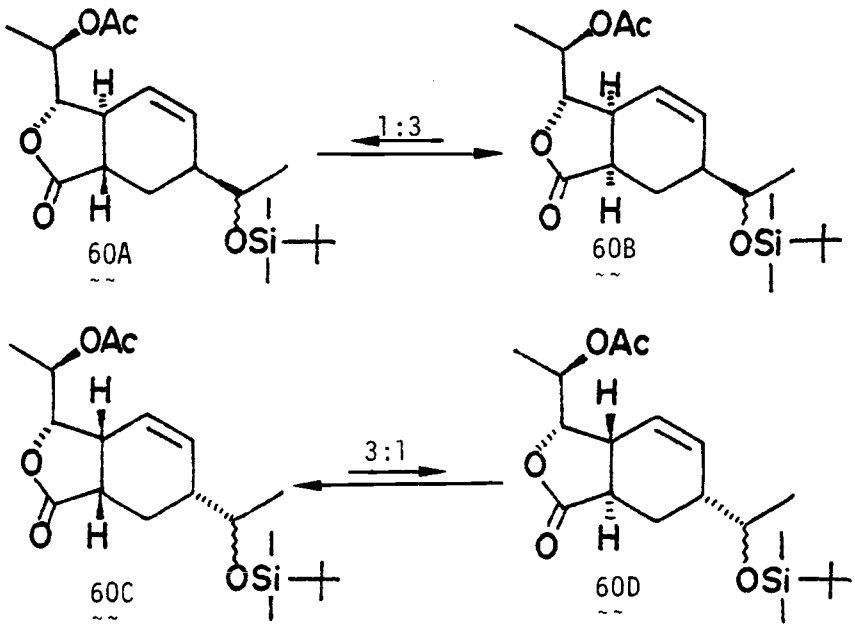


Figure 7. Transition States of the Intramolecular Diels-Alder Reaction.

chromatography, in a ratio of 2.5:2.5:1. These three isomers were shown to be 60A, 60B, and 60C, respectively. The IR spectra of all three compounds showed a carbonyl frequency (1780 cm^{-1}) indicative of a γ-lactone. Also their NMR spectra displayed only two vinyl protons in each case.

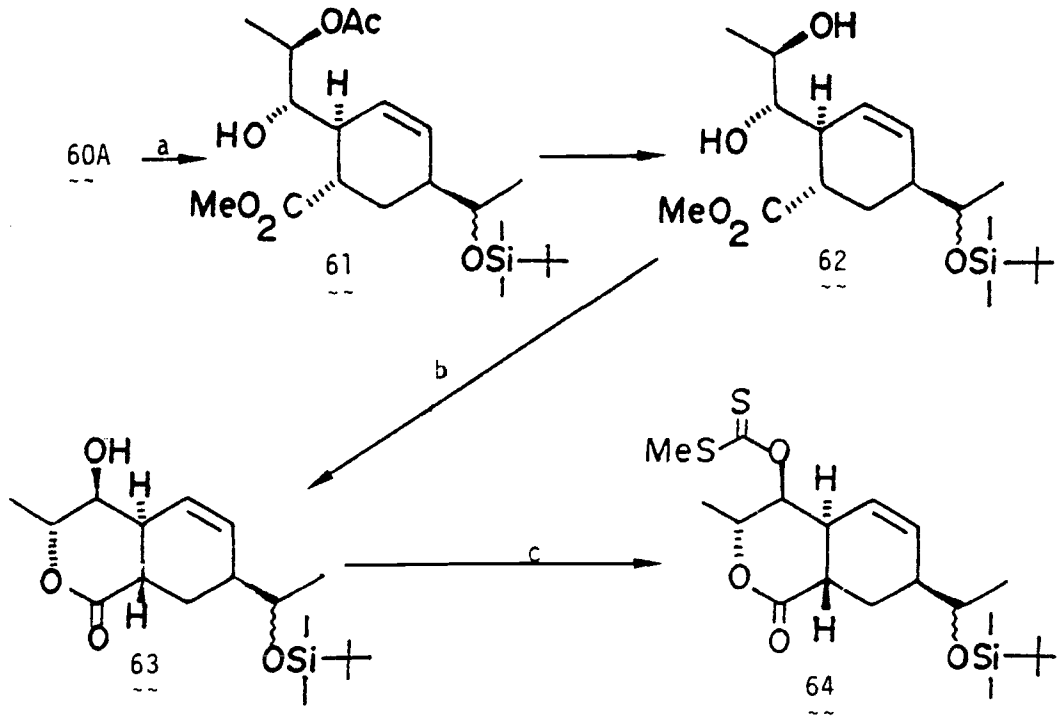
Adducts 60A and 60B were found to be interconvertible by treatment with lithium diisopropylamide. The ratio of epimers (1:3) is



assumed to favor the more thermodynamically stable, cis fused ring system 60B, leaving 60A as the trans isomer.[65] Isomer 60C, under similar equilibrium conditions, supplied a fourth substance 60D,

with a C:D ratio of 3:1. As before, the major epimer was assigned the cis ring fusion.

The assignment of relative configuration to these Diels-Alder adducts is consistent with the foregoing predictions, and is supported by the following chemistry. The trans isomer 60A was treated with potassium carbonate in methanol in an attempt to cleave the acetate. However, the NMR spectrum of the product had retained the three



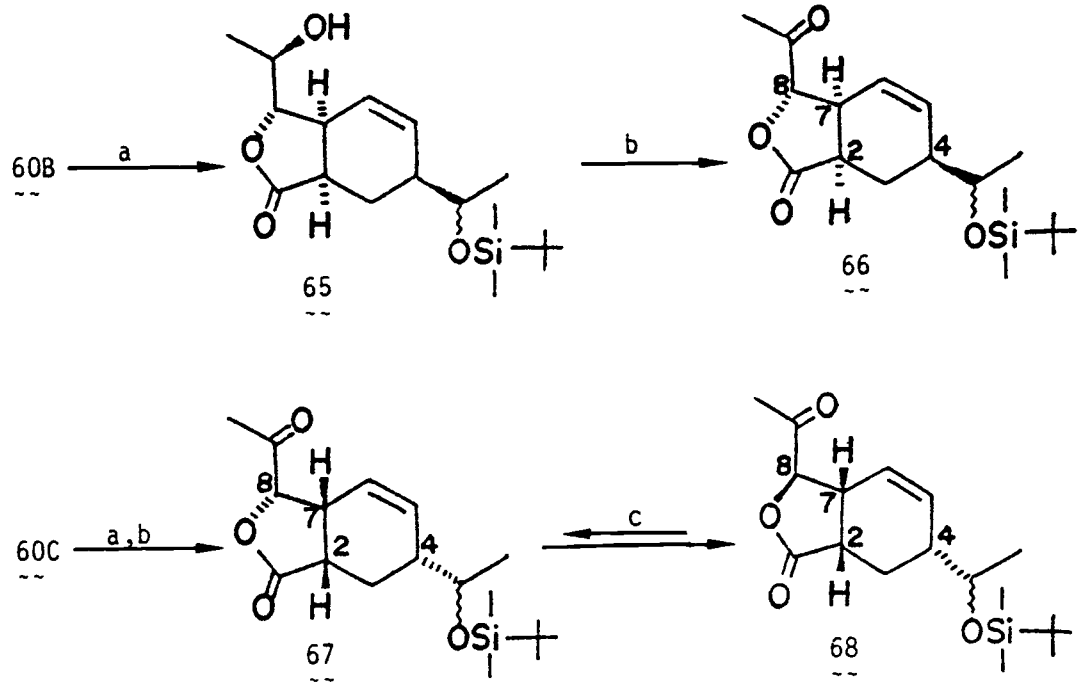
a. K_2CO_3, MeOH; b. PCC; c. NaH, im, THF; CS_2; MeI

proton singlet at δ 2.1 and had acquired a three proton singlet at δ 3.7. From this data, its structure was determined to be the methyl ester 61. Continued hydrolysis in methanol afforded the diol 62, which could

be converted in 99% yield using a catalytic amount of p-toluenesulfonic acid in benzene to the δ-lactone 63. The δ-lactone, which is preferred over a γ-lactone when trans fused to a cyclohexene, is distinguished by an IR band at 1730 cm^{-1}. It was hoped that the free secondary alcohol of 63 could be reductively cleaved, so that this trans fused adduct could provide a viable route to the AB ring system of pillaromycinone. Unfortunately, formation of the methyl xanthate 64 was achieved in only very low yield, and further progress from this point was not feasible.

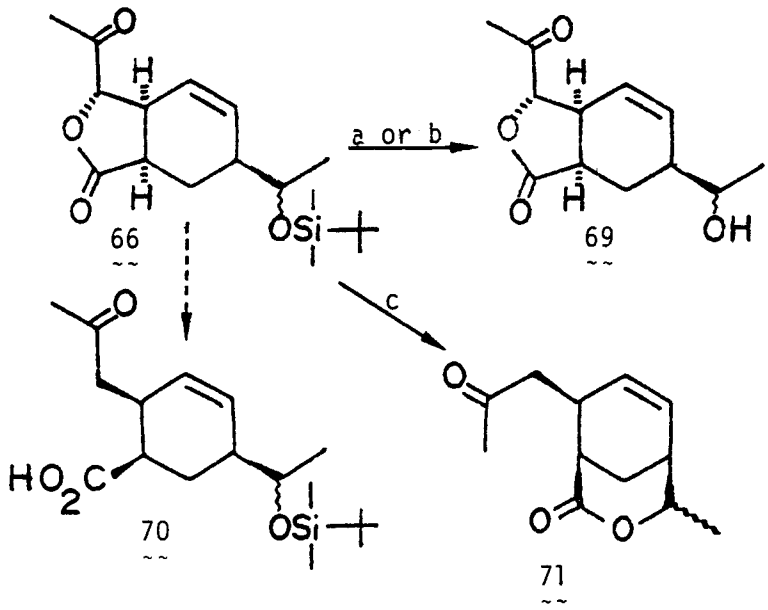
Isomer 60B was likewise treated with potassium carbonate in methanol. The product retained the IR band at 1780 cm^{-1}, but had lost the methyl singlet at δ 2.1 in the NMR spectrum, clearly indicative of the structure 65. Thus, the cis fused γ-lactone was more stable as expected, and was not opened to a methyl ester. The alcohol 65 was oxidized to the ketone 66 using pyridinium chlorochromate in 85% yield. Isomer 60C behaved similarly toward methanolysis and oxidation, yielding the ketone 67. In this substance, the protons H_2 and H_7 exhibited a coupling constant of 10 Hz, consistent with their cis orientation.

The acetyl substituent of 67 resides on the endo face of the bicyclic system, assuming the configuration at C(8) is as drawn. Equilibration of 67 was accomplished using sodium methoxide in methanol, affording a mixture of 68 and 67 in a ratio of 2:1, respectively. The isomer 68 is enantiomeric at C(2,4,7,8) with isomer 66, a fact that was confirmed by their identical TLC behavior and spectral data.



a.K_2CO_3, MeOH; b.PCC c.NaOMe

For the next stage of the synthesis the bond joining the lactone oxygen to the position α to the ketone 66 must be disconnected. Many examples are known in which α-acyloxy ketones are reductively cleaved. One of the milder methods available employs a Cr(II) salt,[66] usually in the presence of an acid. Application of chromous chloride to the reduction of 66 required thorough deoxygenation of the reaction mixture to achieve the blue color characteristic of the reducing Cr(II) solution and, with saturated aqueous ammonium chloride as the proton source, a more polar product was formed as expected. However, a 1780 cm^{-1} band remained in the IR spectrum of the product, whereas the alkylsilyl singlets had disappeared from its NMR spectrum. This



a.Cr^{+2}; b.HOAc, H_2O, THF; c.Zn, HOAc, 80°C

evidence suggested the alcohol 69 as the product of this reaction. The same compound was isolated from treatment of 66 with acetic acid and water in tetrahydrofuran. In order to effect the requisite reaction without cleavage of the silyl ether, the reduction was attempted in non-acidic media. Chromous acetate in dimethylsulfoxide, with a thiol as a hydrogen donor, has been reported to be a neutral reagent for reductive elimination.[67] However, only starting material was recovered with 66 under these conditions.

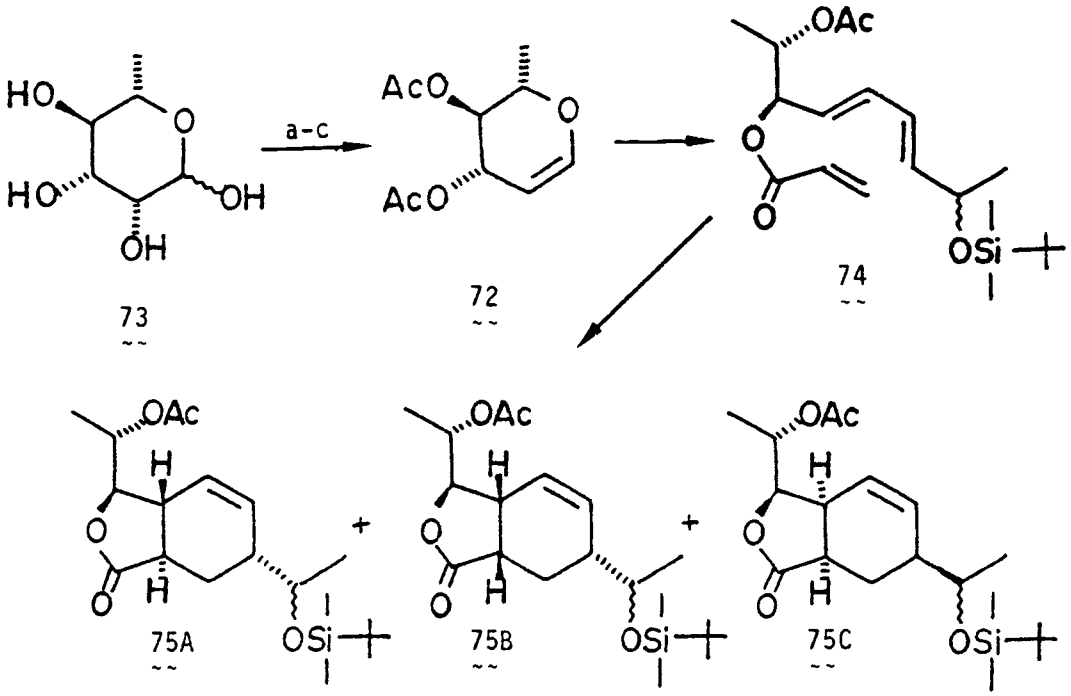
Other transition metals, such as titanium[68] and vanadium[69] possess useful reduced states which might serve for conversion of

66 to the keto acid 70. Unfortunately, their reduction potentials are less than that of chromium: Cr^{+2}, 0.41 V; Ti^{+3}, 0.37 V; V^{+2}, 0.25 V. Zinc, with a reduction potential of 0.76 V, was expected to be more reactive. Upon stirring keto lactone 66 with zinc in acetic acid at room temperature, only starting material was returned. However, upon heating the reaction mixture to 80°C, the required reduction, along with deprotection of the silylether and relactonization to 71 occurred. Although 71 reinforced our proof of the cis orientation of side chains in 66, it did not appear to be a suitable substrate for elaboration of the B ring required for pillaromycinone. In view of the difficulties associated with reduction of the α-acyloxy ketone moiety of 66, and especially since it was now expected that the two major products from the Diels-Alder reaction of 59 belonged to the wrong enantiomeric series for pillaromycinone, attention was turned to a modified route beginning from natural L-rhamnose.

B. AN APPROACH FROM L-RHAMNAL

By analogy with the foregoing results, a sequence originating from the enantiomer of D-glucal would provide an AB ring synthon with the desired absolute configuration. The diacetate of L-rhamnal 72 is the configurational counterpart to 52 and is available from L-rhamnose (73) in three steps in 70% overall yield.[70] Moreover, 72 possesses a C(6) methyl group, which thus circumvents the reductive sequence necessary in the case of glucal.

A sequence exactly parallel with that carried out from D-glucal

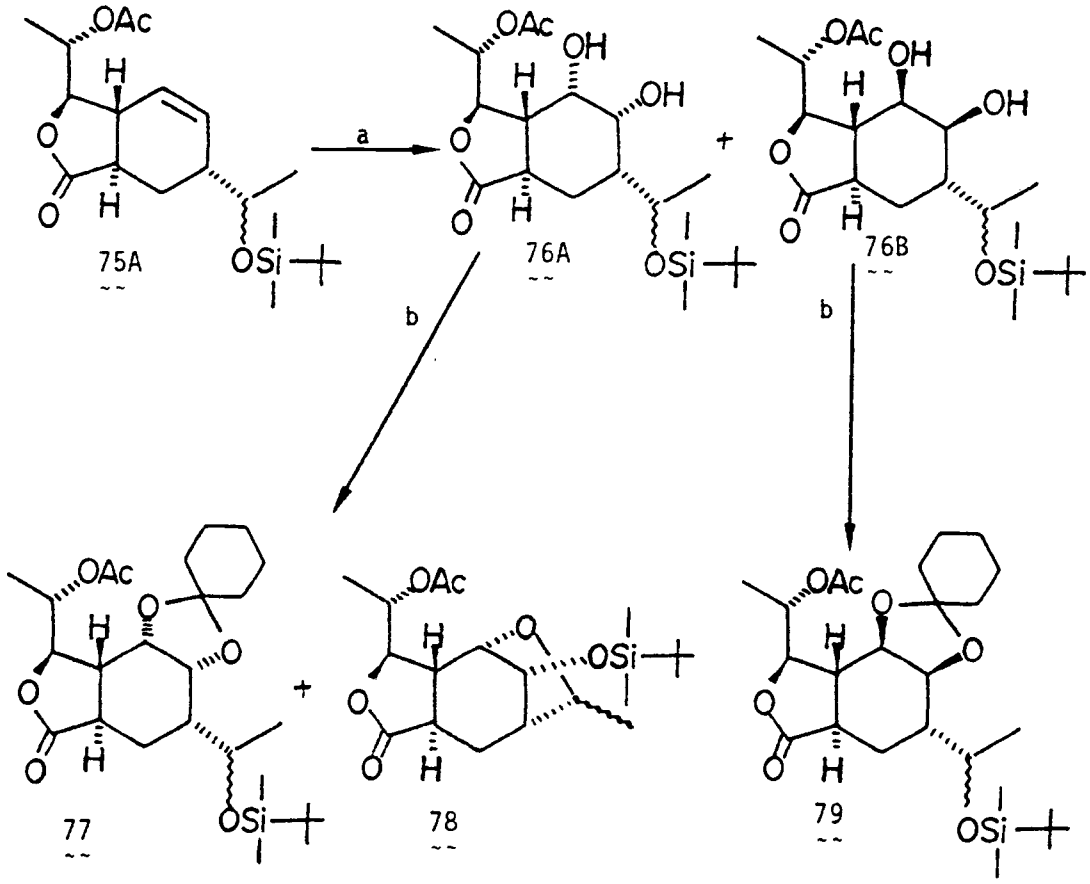


a.Ac_2O, py; b.HOAc, Ac_2O, HBr; c.Zn, HOAc, H_2O, NaOAc, $CuSO_4$

49 led from 72 to the enantiomer of 58. As before, this ketone was reduced and the alcohol protected as its t-butyldimethylsilyl ether 74. The intramolecular Diels-Alder reaction again afforded three adducts, in the ratio 2.5:2.5:1, separable by flash chromatography.

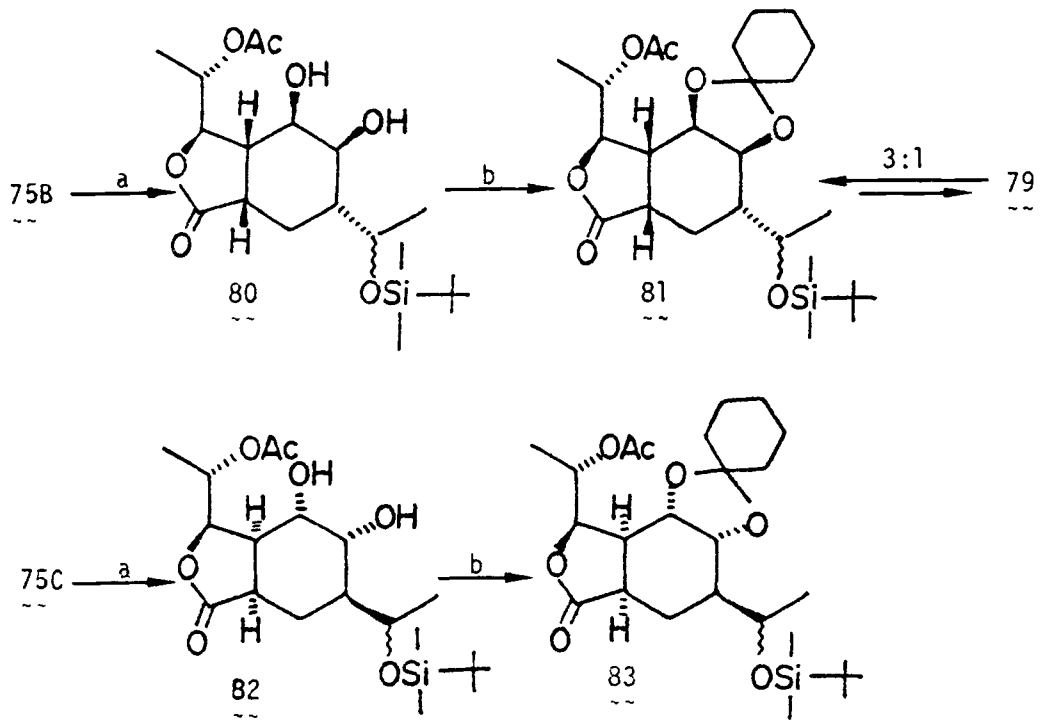
The least polar isomer 75A was hydroxylated using a catalytic amount of osmium tetroxide and N-methylmorpholine-N-oxide. This yielded a 1:1 mixture of two diols, 76A and 76B. Thus, the trans ring fusion of 75A, which leads to a flattened geometry of the bicyclic nucleus, exhibits little face-selectivity of the π bond

toward osmylation. The stereochemistry of the two diols could not be deduced from the data at hand, but exposure of 76A to camphor-sulfonic acid and 1,1-dimethoxycyclohexane afforded the expected cyclohexylidene derivative 77, together with 78. It is clear that 78 can only arise from 76A, in which the siloxyethyl substituent is cis to the diol function. In contrast, protection of 76B gave a single cyclohexylidene derivative 79 in 90% yield.



a.cat OsO_4, NMO, THF, H_2O; b.1,1-dimethoxycyclohexane, CSA

The cis fused Diels-Alder adduct 75B was hydroxylated stereoselectively from the convex face to provide a single diol 80, which was protected as the cyclohexylidene ketal 81. This same cis fused lactone was shown to be the major component of the lithium diisopropylamide-catalyzed epimerization of 79 (81:79, 3:1). The proton coupling across the ring fusion of 81 was 9 Hz, which is consistent with literature values for a cis configuration in this ring system.[65,71]

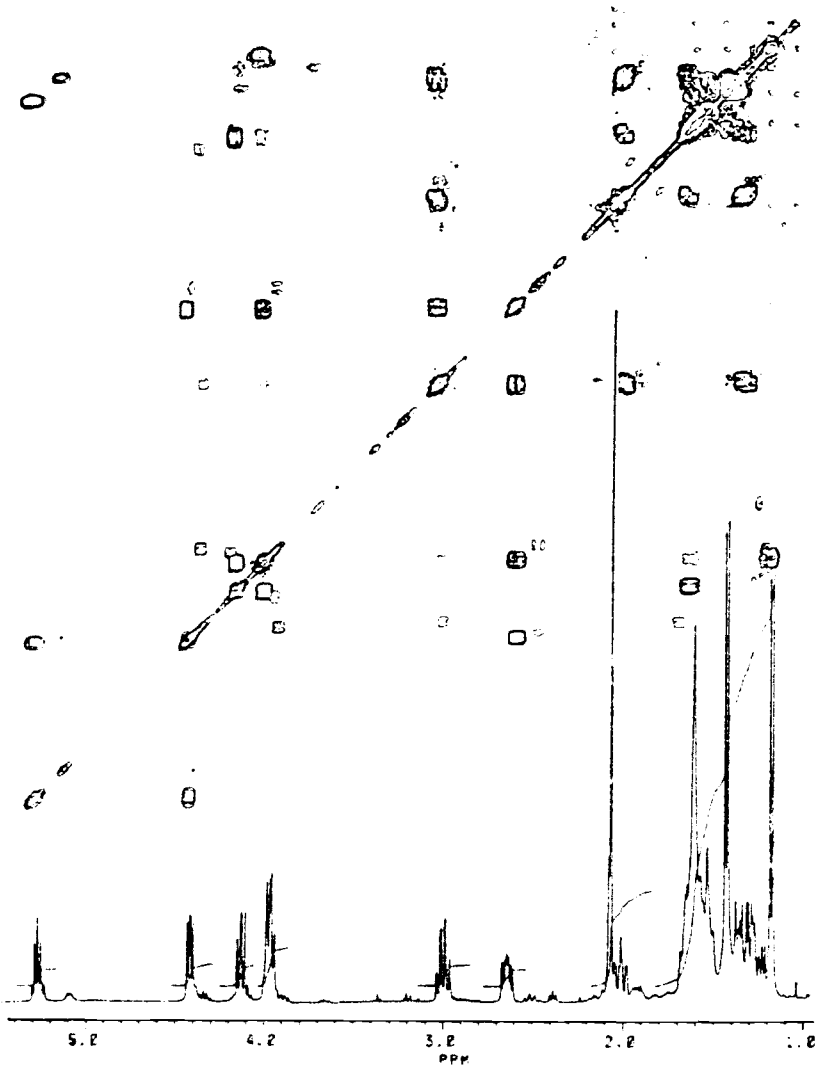


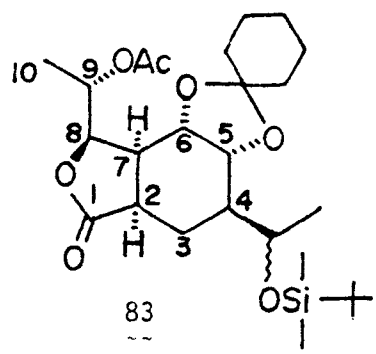
a.cat OsO_4, NMO; b.1,1-dimethoxycyclohexane, CSA

The minor adduct of the Diels-Alder reaction, 75C, was also converted to a single diol 82, thence the ketal 83. Proton coupling across the ring fusion (9 Hz) was again consistent with the proposed cis geometry. Through the use of conventional and autocorrelated, two-dimensional ^{1}H NMR spectroscopy,[72,73] the identity of each proton of compound 83 was assigned. A four-level contour plot of the autocorrelated (COSY), two-dimensional proton NMR spectrum of 83 in deuteriochloroform at 400 MHz is shown in figure 8.

The off-diagonal signals establish proton spin-coupling connectivities. For example, the doublet of doublets at δ 4.42 (J=5,7 Hz). can be seen to be coupled to a doublet of quartets located at δ 5.28 and, further, to a doublet of triplets at δ 2.59 (J=5,9 Hz). The latter resonance is coupled to a quartet at δ 2.99 (J=9 Hz) and a complex multiplet at δ 3.99. This spin-coupling network established the δ 4.42 resonance to be the proton at C(8), and the resonance at δ 2.59 was identified as the proton at C(7).

Of particular interest is the δ 2.99 quartet, which is coupled to the aforementioned δ 2.59 resonance, a doublet of doublet of doublets at δ 1.98 (J=3,9,11 Hz), and a partially obscured resonance at approximately δ 1.3. The quartet at δ 2.99 was therefore assigned to the C(2) proton α to the lactone. The signficant feature of this analysis is that all three vicinal protons couple equally (J=9 Hz) to the C(2) proton, and that one of the protons of the adjacent methylene group is shifted 0.7 ppm further downfield than the other. Three equal coupling constants as large as 9 Hz cannot be achieved with the six-membered ring of 83 in a chair formation. Strong

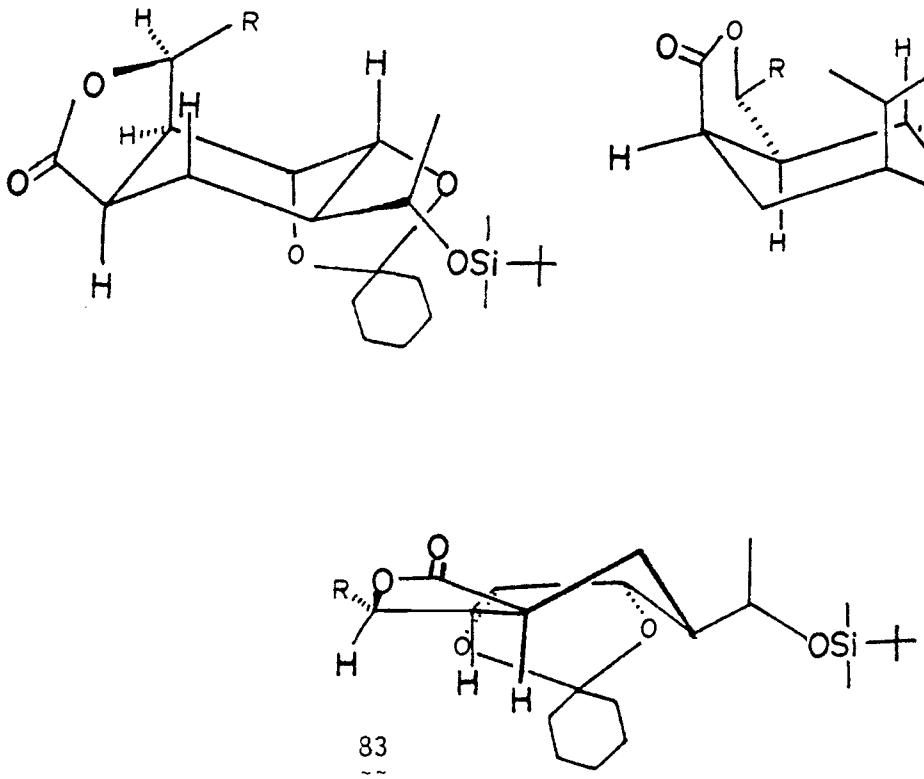




83

Figure 8. Two-Dimensional ^{1}H NMR Spectroscopy (COSY).

1,3-diaxial interactions, as shown in figure 9, further suggest that a chair conformation is unlikely. To alleviate these diaxial interactions, a twist boat conformation is apparently adopted, placing all five substituents pseudo equatorial on the six-membered ring. The proton at C(2) may then be coupled equally to the three vicinal protons. The equatorial proton ($H_{3\alpha}$) lies in the deshielding cone of the lactone carbonyl, thus explaining the downfield shift. Corroboration of the $H_{3\alpha}$ assignment follows from its 3 Hz coupling to the C(4) proton, a value typical of axial-equatorial interaction.



83

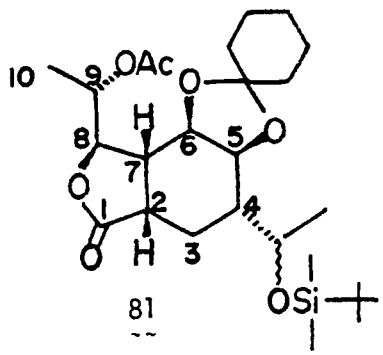
Figure 9. Possible Conformations of Compound 83.

The proton NMR spectra of isomers 81 and 83 are compared in Table III. These two diastereomers possess the same relative configuration around the six-membered ring, differing only about the C(7-8) bond. Their proton NMR spectra are very similar, including the appearance of a quartet at ca. 2.9 ppm. One significant difference, however, is the coupling of H(7) to H(8). The stereochemistry of isomer 81 was apparent from the $J_{7,8}$ value of 2 Hz, which implies a trans relationship of H(7) and H(8).[74,75] The larger $J_{7,8}$ value of 5 Hz for isomer 83 is consistent with a cis relationship for H(7) and H(8). The coupling data, while not entirely conclusive, strongly suggest that the correct absolute configuration required for pillaromycinone is generated at C(7) by the route from L-rhamnal.

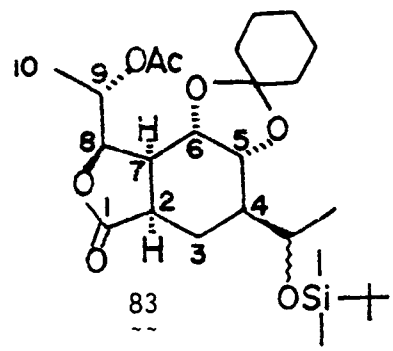
At the next stage of the synthesis, the original chiral centers of the carbohydrate are removed, leaving only those transferred as a result of the intramolecular Diels-Alder and subsequent reactions. In a sense, the sugar has served as a stereochemical template from which configuration at the new centers of the AB ring has been derived.

With the requisite carbon skeleton established, construction of the B ring was the next task. Employing reactions previously worked out in the D-glucal series, ketone 84 was obtained from the acetoxy lactone 81 in high yield. The proton at C(8) in 84 appears as a doublet at δ 4.81 (J=2 Hz), indicative of a trans relationship for H(7) and H(8).

Previous efforts to reduce the α-acyloxy ketone moiety of 66 to a δ-keto acid either failed or simultaneously removed the silyl



81



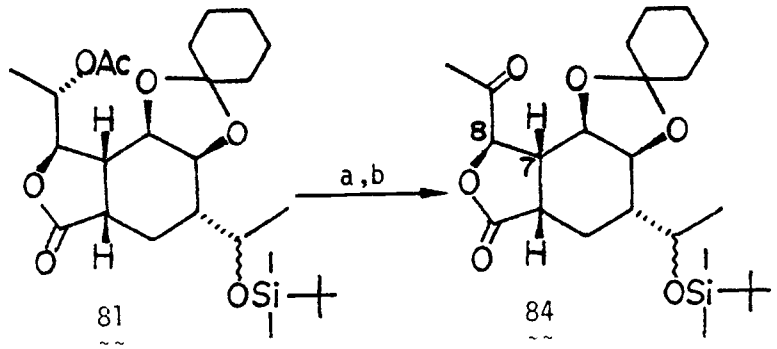
83

Table III. Proton Assignments for 81 and 83 (400 MHz in $CDCl_3$).

81	H_9	H_8	H_5	$H_{6,11}$	H_2	H_7	OAc	$H_{3\beta}$	Me_{10}	Me_{12}
δ	5.12	4.39	4.34	3.95	2.90	2.45	2.04	1.89	1.28	1.21
multiplicity	dq	dd	dd	m	q	dt	s	ddd	d	d
integral	1H	1H	1H	2H	1H	1H	3H	1H	3H	3H
J	4,7	2,4	7,8		9	2,9		2,9,12	7	6

83	H_9	H_8	H_5	$H_{6,11}$	H_2	H_7	OAc	$H_{3\alpha}$	Me_{10}	Me_{12}
δ	5.28	4.42	4.15	3.99	2.99	2.59	2.03	1.98	1.41	1.17
multiplicity	dq	dd	t	m	q	dt	s	ddd	d	d
integral	1H	1H	1H	2H	1H	1H	3H	1H	3H	3H
J	6,7	5,7	8		9	5,9		3,9,11	6	6

protecting group. Consequently, further studies were undertaken with the goal of effecting selective conversion of 84 to 85. The use of two equivalents of lithium dimethylcuprate has been reported to accomplish reductive elimination of α-acyloxy ketones.[76,77] The reduction potential of a cuprate is ca. 2.3 V, which is much larger than that of Zn, 0.7 V. It is presumed that reduction by cuprate



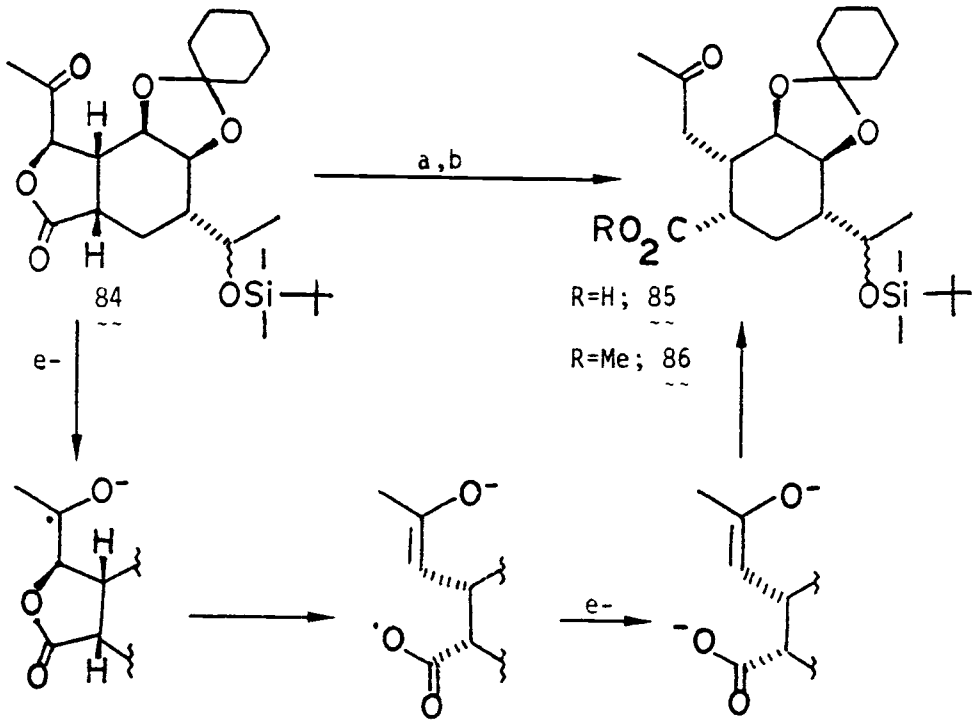
81 84

a. K_2CO_3, MeOH; b. PCC, CH_2Cl_2

proceeds by electron transfer to the ketone, forming a radical anion and in figure 10, this process is applied to 84. After elimination to generate the carboxyl radical and the ketone enolate, a second electron transfer leads to the carboxylate anion which furnishes the keto acid 85 after acidification. Unfortunately, the reaction was not clean in the case of 84 and afforded only 37% of the keto ester 86 after methylation and purification.

Not only transition metals, but also lanthanide derivatives have been employed as reducing agents in organic synthesis.[78] Divalent lanthanides such as samarium and ytterbium diiodide have been

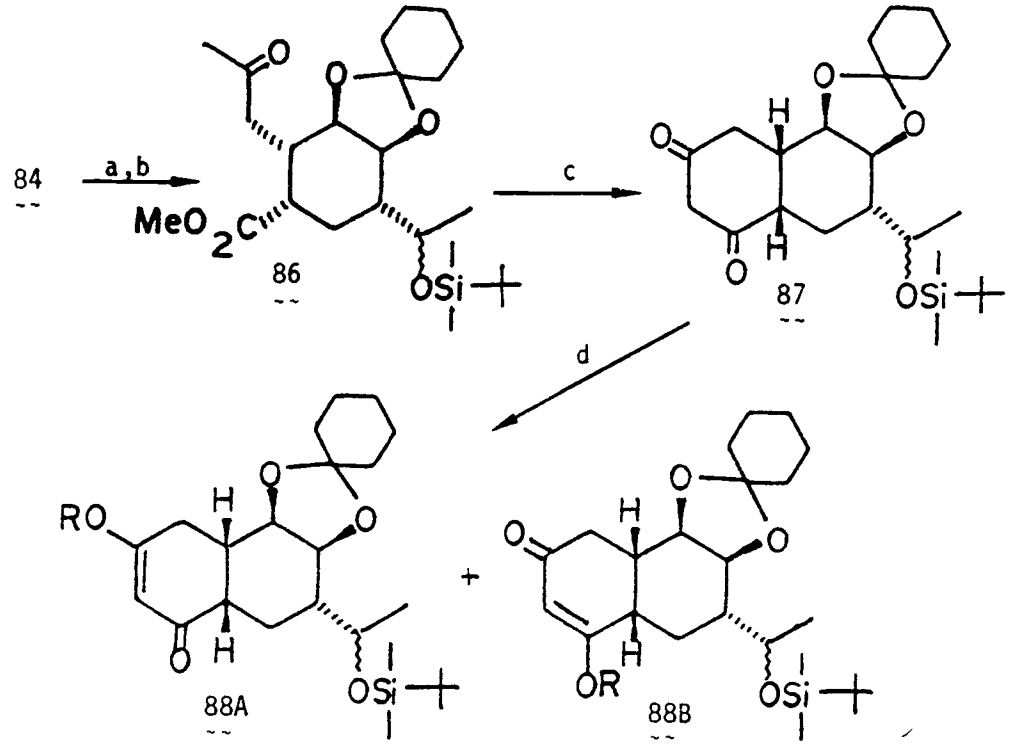
prepared and possess moderate reduction potentials, 1.55 and 1.15 V respectively. In the present study, the keto lactone 84 was stirred with samarium diiodide and a catalytic amount of ferric chloride to provide, after methylation, 66% of 86, together with 10% of recovered starting material.



a.$LiMe_2Cu$(2eq), THF, DMS; b.CH_2N_2

Figure 10. Mechanism of the Cuprate Reduction.

With keto ester 86 in hand, closure of the B ring was the final hurdle in our path to the AB ring synthon. Following a procedure described by Corey,[79] intramolecular acylation of 86 was attempted with two equivalents of sodium hydride in refluxing benzene with a catalytic amount of methanol, but the reaction was very sluggish.



a.SmI_2, THF; b.CH_2N_2; c.KO$\underline{t}$Bu, $\underline{t}$BuOH, benzene; CH_2N_2

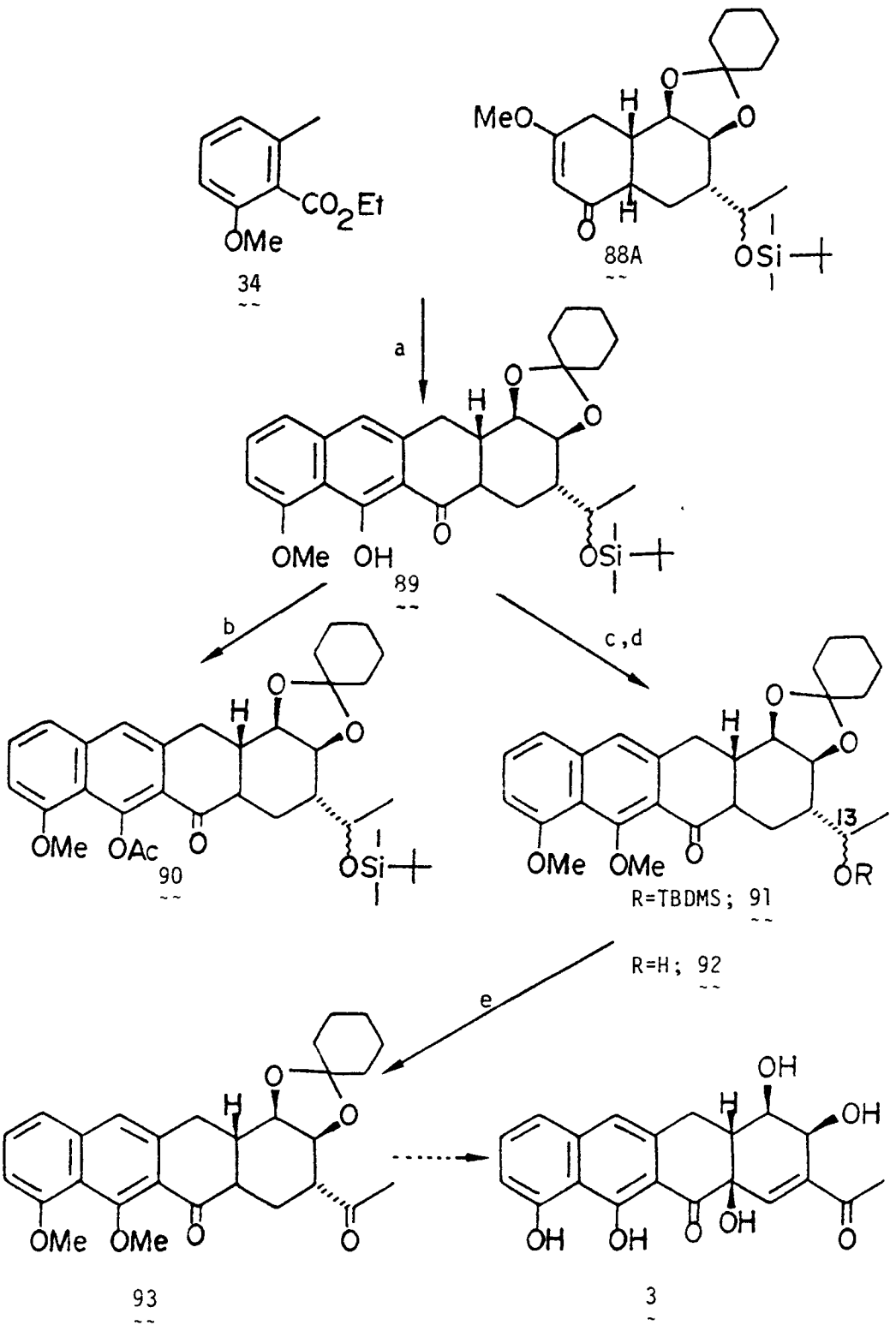
By contrast, addition of potassium $\underline{t}$-butoxide in $\underline{t}$-butanol to 86 gave, after five minutes, a polar, UV-active material. Methylation of the product with diazomethane afforded two separable, methyl enol ethers in a ratio of 2:1, in an overall 70% yield based on 86. The least polar, major isomer was assumed to be 88A, based on a comparison of TLC polarity with other 3-alkoxy-2-cyclohexen-1-one derivatives and their 1-alkoxy counterparts.[79,80] Also, the 3-ketone was expected to be the more accessible position for methylation on steric grounds. A similar ratio of products was obtained employing dimethyl sulfate or diethyl sulfate and potassium carbonate with 87. Trimethyl orthoformate with pyridinium $\underline{p}$-toluenesulfonate gave no trace of an enol

ether with 87. It was hoped that a more bulky alkyl substituent would favor O-alkylation at C(3) over C(1). However, attempts to form the isopropyl enol ether of 87 were unsuccessful using a base and isopropyl bromide.

IV. SYNTHESIS OF THE TETRACYCLIC NUCLEUS

Having gained access to the chiral enol ether 88A constituting the AB ring system of pillaromycinone, the stage was set for coupling with the toluate 34 to assemble the entire carbon skeleton of the aglycone. The anion of 34 was generated using two equivalents of lithium diisopropylamide and was condensed with the enol ether 88A at -78°C. After briefly allowing the reaction mixture to warm to room temperature, acidification afforded a highly fluorescent material 89 in 32% yield. The greenish-yellow compound was difficult to purify, but was characterized by a band at 1625 cm^{-1} in its IR spectrum, typical for a chelated carbonyl.[21] Also, the UV spectrum displayed an absorption maximum at 398 nm.[22] Characterization of the tetracyclic product 89 was completed after acetylation, which afforded the naphthacenone 90. Also, the dimethoxynaphthacenone 91 was obtained from 89 by treatment with dimethyl sulfate. To our surprise, 91 was more polar on TLC than 89 with ethyl acetate and hexane as the chamber solvents, supporting the claim of strong chelation between the phenolic hydroxyl and the carbonyl group in 89. Removal of this chelation upon methylation is also apparent from a shift of the absorption maximum in the UV spectrum of 91 to 341 nm.[21]

To this point in the synthesis a pair of epimeric compounds has been carried through the sequence. In order to simplify this stereochemical dichotomy, a conversion of the center at C(13) to a ketone was effected. Thus the dimethoxynaphthacenone 91 was treated with



a.LDA, THF; b.DMAP, NEt_3, Ac_2O; c.Me_2SO_4, K_2CO_3; d.n-BuNF; e.PCC

tetra-n-butylammonium fluoride to remove the silyl ether. Observation of the reaction mixture by TLC revealed the expected transformation of 91 to a more polar compound. The presumed alcohol 92 was oxidized cleanly to the ketone 93 with pyridinium chlorochromate. Although the scarcity of material at this stage prevented a full characterization of 93, its UV spectrum remained in agreement with the naphthacenone chromophore, while its NMR spectrum provided evidence for a methyl ketone with a singlet at δ 2.3.

Although a total synthesis of pillaromycinone remains to be completed, the approach described herein exemplifies an attractive, convergent strategy for assembly of the tetracyclic nucleus of the aglycone. Also, this sequence demonstrates the use of an asymmetric intramolecular Diels-Alder reaction for introduction of stereochemistry into the A ring of pillaromycinone. In addition, a novel samarium diiodide reduction, as well as an interesting, intramolecular Claisen condensation, were exploited in this work. Completion of this route to pillaromycinone requires C(12a) hydroxylation and installation of the C(1-2) double bond. These modifications to 93 will be undertaken by subsequent investigators.

V. EXPERIMENTAL

Solvents were dried by distillation shortly before use from an appropriate drying agent. Ether and tetrahydrofuran were distilled from sodium/benzophenone under nitrogen. Benzene and toluene were distilled from sodium/benzophenone under nitrogen and stored over 3 Å molecular sieves. Methylene chloride, acetonitrile, dimethylformamide, pyridine, 2,6-lutidine, and other amines were distilled from calcium hydride under nitrogen. Methanol and ethanol were distilled from magnesium turnings.

Unless otherwise noted, starting materials were obtained from commercial suppliers and used without further purification. "Ether" used in workups refers to anhydrous diethyl ether, which was supplied by Mallinckrodt. Brine refers to a saturated aqueous solution of sodium chloride. For isolation of reaction products, the solvent was removed by rotary evaporation at water aspirator pressure and residual solvent was removed under vaccuum, at less than 1 mm. Reaction flasks and syringes were dried in an oven (at 165°C) overnight and allowed to cool in a dessicator over anhydrous calcium sulfate prior to use. Alternatively, flasks were flame-dried under a stream of nitrogen.

Analytical thin-layer chromatography (TLC) was conducted on 2.2 x 7.5 cm precoated TLC plates (silica gel 60 F-254, layer thickness 0.2 mm, manufactured by E. Merck). Silica gel columns for flash chromatography utilized E. Merck silica gel 60 (230-400 mesh ASTM). Alumina refers to the Brockmann activity I neutral material

manufactured by M. Woelm. High pressure liquid chromatograph (HPLC) was performed with a Waters M-45 solvent delivery system equipped with a Waters semipreparative silica column and an ISCO variable-wavelength ultraviolet absorption detector.

All melting points and boiling points are uncorrected. Infrared (IR) spectra were determined on a Perkin-Elmer Model 727B spectrophotometer. Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded on either a Varian EM-360A, HA-100, FT-80A, NR-80F, or Bruker AM-400 spectrometers. Chemical shifts are expressed in ppm downfield from internal tetramethylsilane (δ 0.00). ^{1}H NMR data are tabulated in order: multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; p, pentuplet; m, multiplet), number of protons, coupling constant in Hertz. Ultraviolet (UV) spectra were measured on a Varian Cary Model 210 spectrophotometer. Optical rotations were measured in 1-dm cells of 1-mL capacity using a Perkin-Elmer Model 243 polarimeter. Low resolution mass spectra (MS) were obtained with either a Varian MAT CH-7 or a Finnigan Model 4500 spectrometer at an ionization potential of 70 eV. Exact mass determinations were performed on a CEC-110C spectrometer at an ionization potential of 70 eV. Elemental analyses were performed by MicAnal, Tucson, Arizona.

Ethyl 2-Methoxy-6-methylbenzoate (34)

To a stirred solution of sodium (0.33 g) in ethanol (100 ml) was added ethyl acetoacetate (65.66 g, 0.50 mol). The solution was cooled in an ice-bath and a solution of crotonaldehyde (35.00 g, 0.50 mol) in ethanol (40 mL) was added over 1 h. The faint yellow solution was allowed to stir overnight. The solution was cooled to 0°C and saturated with dry hydrogen bromide gas (ca. 20 min), then left under argon at room temperature overnight. The reaction was followed by observation of the disappearance of the singlet at 2.2 ppm (CH_3-C=O) from the NMR spectrum. Evaporation of the solvent and vacuum distillation of the residual liquid yielded 46.77 g (52%) of ethyl 6-carboxy-5-methyl-2-cyclohexen-1-one: bp 76-84°C/0.47 mm; IR (film) 1750, 1690, 1320, 1260 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.08 (d, 3H, J=6), 1.29 (t, 3H, J=8), 1.92-2.80 (m, 3H), 3.15 (d, 1H, J=12), 4.27 (q, 2H, J=8), 6.07 (ddd, 1H, J=1,1,10), 7.02 (ddd, 1H, J=3,3,10); MS m/z 182 (M^+).

To a solution of cyclohexenone ester (20.00 g, 0.11 mol) in carbon tetrachloride (100 mL) in an ice-bath under nitrogen was added bromine (17.47 g, 0.11 mol) in acetic acid (100 mL). The bromine color faded instantly as it was added. The addition funnel was rinsed with carbon tetrachloride and the mixture was stirred for 0.5 h. The reaction was refluxed for 12 h under a stream of nitrogen to remove hydrogen bromide. The mixture was cooled to room temperature and methylene chloride (125 mL) and water (125 mL) were added. The aqueous layer was separated and the organic layer was washed several

times with saturated sodium bicarbonate to remove traces of acetic acid. The organic layer was dried (magnesium sulfate) and evaporated. The residue was steam distilled to give a colorless, sweet-smelling solid. Recrystallization from methanol/water yielded ethyl 2-hydroxy-6-methylbenzoate. The phenol was dissolved in ether, dried (magnesium sulfate) and evaporated to remove water of recrystallization, leaving 12.12 g (61%) of the benzoate: ^{1}H NMR ($CDCl_3$) δ 1.39 (t, 3H, J=8), 2.51 (s, 3H), 4.43 (q, 2H, J=8), 6.68 (broad d, 1H, J=8), 6.84 (broad d, 1H, J=8), 7.23 (t, 1H, J=8).

A solution of the benzoate (7.82 g, 0.04 mol) in acetone (60 mL) containing dimethyl sulfate (13.33 g, 0.06 mol) and potassium carbonate (8.30 g, 0.06 mol) was refluxed for 17 h. The reaction mixture was filtered and the acetone was evaporated. The oil was taken up in ether (45 mL) and excess triethylamine (6 mL) was added. The quarternary ammonium salt was precipitated and after 1 h was filtered off. Water (3 x 25 mL), 10% hydrochloric acid, and brine were used to wash the organic layer, which was dried (magnesium sulfate) and evaporated to give a yellow oil. The oil was distilled, yielding 34 as a colorless oil (7.54 g, 88%): bp 78-83°C/0.35 mm; IR (film) 1728, 1585, 1270, cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.39 (t, 3H, J=7), 2.31 (s, 3H), 3.80 (s, 3H), 4.43 (q, 2H, J=7), 6.74 (d, 1H, J=8), 6.80 (d, 1H, J=8), 7.22 (t, 1H, J=8).

2-Carboethoxy-3-methoxybenzyl phenyl sulfoxide (23).

The toluate 34 (0.970 g, 5.000 mmol) in dry tetrahydrofuran (6 mL) was added under nitrogen to a solution of lithium diisopropylamide (5.200 mmol) in dry tetrahydrofuran (10 mL) cooled to -78°C.

The resulting deep red solution was transferred via cannula to a solution of phenyl disulfide (1.200 g, 5.500 mmol) in dry tetrahydrofuran (10 mL) cooled to -78°C. After the addition, 5% hydrochloric acid (10 mL) was added to the cold solution. The reaction mixture was then added to additional 5% hydrochloric acid (50 mL) and ether (75 mL). The organic layer was separated and washed successively with 5% aqueous sodium hydroxide (2 x 25 mL), brine (25 mL), and water (25 mL). Upon drying (magnesium sulfate), evaporation, and chromatography (100 g SiO_2, chloroform), 1.308 g (84%) of 2-carboethoxy-3-methoxybenzyl phenyl sulfide was obtained: IR (film) 1748, 1600, 1488, 1280, 1085 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.32 (t, 3H, J=7), 3.75 (s, 3H), 4.14 (s, 2H), 4.39 (q, 2H, J=7), 6.77 (d, 1H, J=8), 6.86 (d, 1H, J=8) 7.22 (m, 6H).

The thioether (1.308 g, 4.300 mmol) in methanol (15 mL) was added to sodium metaperiodate (1.112 g, 5.200 mmol) in 30 mL of water/methanol (1:1) at 0°C. After 9.5 h, the reaction was filtered and extracted with methylene chloride (4 x 20 mL). After drying the organic solution (magnesium sulfate), it was evaporated to give an oil which was chromatographed (40 g SiO_2, 2.5% ethanol/chloroform) to afford 1.128 g (81%) of 23: IR (film) 1724, 1585, 1475, 1280, 1070 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.40 (t, 3H, J=8), 3.84 (s, 3H), 4.13 (d, 2H, J=7), 4.43 (q, 2H, J=8), 6.66 (d, 1H, J=8), 6.92 (d, 1H, J=8), 7.49 (broad s, 6H); MS m/z 302 (M^+), 165.

Ethyl 1,8-Dimethoxy-3-methyl-2-naphthoate (25)

To diisopropylamine (0.383 g, 3.800 mol) in dry tetrahydrofuran (3 mL) under nitrogen was added n-butyl lithium (2.38 mL, 3.80 mmol) at 0°C. After 15 min, the solution was cooled to -78°C and a solution of 23 (0.564 g, 1.800 mmol) in dry tetrahydrofuran (5 mL) was added, giving a dark reaction mixture. Ethyl crotonate (0.490 g, 4.300 mmol) was added and the mixture was allowed to warm to room temperature for 2 h, and was then refluxed for 3 h. Upon cooling, the reaction was quenched by addition of 5% hydrochloric acid (15 mL) and extracted with ether (25 mL). The organic layer was washed with water (2 x 10 mL), 50% aqueous sodium bicarbonate (1 x 10 mL), and brine. The organic portion was dried (magnesium sulfate) and evaporated. The residue was chromatographed (20 g SiO_2, chloroform) to yield 0.242 g (52%) of ethyl 2-carboxy-8-methoxy-3-methyl-1-naphthol: IR (film) 3370, 1730, 1645, 1265 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.52 (t, 3H, J=7), 2.55 (s, 3H), 4.11 (s, 3H), 4.56 (q, 2H, J=7), 7.15 (m, 4H).

The naphthol (0.441 g, 1.700 mmol), potassium carbonate (0.304 g, 2.200 mmol), and dimethyl sulfate (0.252 g, 2.000 mmol) were refluxed in acetone (30 mL) for 14 h. Upon cooling, the mixture was filtered and the solvent was evaporated. The oil was taken up in ether (20 mL) and excess triethylamine was added. The quarternary ammonium salt was precipitated and after 1 h was filtered off. The organic portion was washed with water (3 x 15 mL), 10% hydrochloric acid, and brine. After drying (magnesium sulfate) and evaporation of the solvent, 0.438 g (95%) of 25 was obtained as yellow crystals: mp 56-59°C;

IR (KBr) 1725, 1575, 1464 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.43 (t, 3H, J=7), 2.44 (s, 3H), 3.92 (s, 3H), 4.00 (s, 3H), 4.49 (q, 2H, J=7), 6.7-6.9 (m, 1H), 7.2-7.5 (m, 3H); MS m/z 274 (M^+), 229.

3-(2-Carboethoxy-3-methoxybenzyl)-2-cyclohexen-1-one (36) and 3,4-Dihydro-9-hydroxy-8-methoxy-1(2H)-anthracenone (37).

1. To a solution of lithium diisopropylamide (0.66 mmol) in dry tetrahydrofuran (1 mL) at -78°C under argon was added a solution of toluate 34 (0.064 g, 0.330 mmol) in dry tetrahydrofuran (1.5 mL). After 20 min, the red solution was cannulated into a solution of 3-methoxy-2-cyclohexen-1-one (0.028 g, 0.220 mmol) in dry tetrahydrofuran (1.5 mL) and the mixture was slowly allowed to warm to room temperature over 2.2 h. Quenching with 5% hydrochloric acid at 0°C gave a fluorescent yellow solution, which was extracted with ether (2 x). The combined organic layers were washed with water and brine. After drying (sodium sulfate), the solvent was removed and the residue was flash chromatographed (10mm x 4" SiO_2, 20% ethyl acetate/hexane). A colorless oil, 36, was obtained in 35% yield, along with the less mobile 37 (28%) as a yellow crystalline solid. Compound 36: IR ($CHCl_3$) 1720, 2660, 1585, 1200, 650 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.31 (t, 3H, J=7), 1.6-2.2 (m, 6H), 3.49 (broad s, 2H), 3.81 (s, 3H), 4.33 (q, 2H, J=7), 5.79 (t, 1H, J=1), 6.7-7.7 (m, 3H); MS m/z 288 (M^+), 243, 149; exact mass m/z 288.136 (calcd for $C_{17}H_{20}O_4$: 288.136). Com-

Compound 37: mp 142-144°C; IR ($CHCl_3$) 1622, 1578, cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.12 (q, 2H, J=7), 2.74 (t, 2H, J=7), 2.97 (t, 2H, J=7), 3.97 (s, 3H), 6.72 (d, 1H, J=8), 6.89 (s, 1H), 7.12 (d, 1H, J=8),

7.18 (s, 1H), 7.39 (t, 1H, J=8); UV ($CHCl_3$) λ_{max} 268, 397 nm; MS m/z 242 (M^+), 196, 149; exact mass m/z 242.094 (calcd for $C_{15}H_{14}O_3$: 242.094).

2. To 36 (0.0085 g, 0.0290 mmol) in dry ethanol (2 mL) was added at 25°C a 0.14 M solution of sodium ethoxide in ethanol (0.40 mL, 0.06 mmol). The reaction was warmed to 45°C overnight, then cooled and worked up as before by acidification and extraction. Flash chromatography (7mm x 2" SiO_2, 20% ethyl acetate/hexane) provided 37 as a yellow residue (0.0017 g, 24%).

2-Phenylselenyl-2-cyclohexen-1-one (42)

Freshly distilled pyridine (0.47 mL, 5.70 mmol) was added to a solution of phenylselenyl chloride (1.05 g, 5.50 mmol) in methylene chloride (50 mL) and the reaction mixture was stirred for 10 min, by which time the mixture had changed from a deep red to a lighter red color. Cyclohexenone (0.47 g, 5.00 mmol) was added under nitrogen at room temperature. After 12 h, the reaction was quenched with 10% hydrochloric acid. The organic layer was separated and dried (magnesium sulfate). Upon solvent evaporation, the residue was flash chromagraphed (30mm x 5.5" SiO_2, 50% ethyl acetate/hexane) to yield 1.01 g (40%) of 42 as pale yellow crystals. Recrystallization of a portion of this material from ethyl acetate/hexane gave colorless crystals: mp 64.5-65.5°C; ^1H NMR ($CDCl_3$) δ 2.00-2.55 (m, 4H), 2.70 (t, 2H, J=6), 6.25-6.75 (m, 5H), 6.52 (t, 1H, J=4); MS m/z 252 (M^+), 157, 115, 91, 77.

3-(2-Carboethoxy-3-methoxybenzyl)-2-phenylselenyl-1-cyclohexanone (43).

The toluate 34 (0.058 g, 0.300 mmol) in dry tetrahydrofuran (1 mL) was added to a solution of lithium diisopropylamide (0.480 mmol) in dry tetrahydrofuran (2 mL) at -78°C under argon. To the resulting red solution was added a solution of 42 (0.075 g, 0.300 mmol) in dry tetrahydrofuran (1 mL). The mixture was warmed slowly to room temperature for 7 h, then quenched with 5% hydrochloric acid. The mixture was extracted with ether (3 x) and the combined organic portions were washed with water and brine. After drying (magnesium sulfate), the solvent was evaporated and the residue was flash chromatographed (20mm x 5.5" SiO_2, 10% ethyl acetate/hexane) to supply 0.026 g (20%) of 43 as an oil: IR ($CHCl_3$) 1715, 1580, 1465, 1270 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.48 (t, 3H, J=7), 1.8-3.4 (m, 9H), 3.92 (s, 3H), 4.3-4.7 (m, 3H), 6.7-7.7 (m, 8H); MS m/z 446 (M^+), 401, 253, 243, 194, 148, 77; exact mass m/z 446.025 (calcd for $C_{23}H_{26}O_4Se$: 446.024).

1,5-Anhydro-D-arabino-hex-1-enitol (D-Glucal, 49)

To the tri-O-acetyl-D-glucal 53 (5.00 g, 18.36 mmol) in dry methanol (90 mL) was added 0.30 M sodium methoxide in methanol (3.00 mL, 1.90 mmol) under nitrogen. After 48 h at room temperature, the solution was treated with carbon dioxide and the solvent was then removed. The dry residue was washed with hot ethyl acetate (250 mL) and evaporation of these washings gave 2.70 g (100%) of 49 as a colorless glass: mp 57-58°C; IR ($CHCl_3$) 3400 broad, 1655 cm^{-1}; ^1H NMR (D_2O) δ 3.25-4.25 (m, 5H), 4.61 (dd, 1H, J=2,6), 6.26 (dd, 1H, J=1,6); MS m/z 146 (M^+), 73.

3,4-Di-O-acetyl-1,5-anhydro-1,2,6-trideoxy-D-arabino-hex-1-enitol (6-Deoxy-3,4-di-O-acetyl-D-glucal, 52).

To a solution of D-glucal 49 (7.50 g, 51.40 mmol) in dry pyridine (90 mL) was added gradually, under ice-cooling, a solution of p-toluenesulfonyl chloride (10.70 g, 56.50 mmol) in pyridine (40 mL) and the mixture was left for 19.5 h. Acetic anhydride (120 mL) was added to the reaction mixture, which was left for 48 h. The mixture was poured into ice-water (430 mL) and allowed to stand for 3 h. This resulted in a gummy solid, which was filtered and recrystallized from ethanol to provide 8.79 (47%) of 6-O-tosyl-3,4-di-O-acetyl-D-glucal: IR ($CHCl_3$) 1740, 1645, 1225 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.00 (s, 3H), 2.01 (s, 3H), 2.41 (s, 3H), 4.18 (m, 3H), 4.77 (ddd, 1H, J=1,3,7), 5.13 (m, 2H), 6.28 (dd, 1H, J=1,7), 7.26 (broad d, 2H, J=9), 7.73 (broad d, 2H, J=9).

The tosylate (3.28 g, 8.44 mmol) and sodium iodide (3.78 g, 25.22 mmol) in acetone (90 mL) were refluxed for 46 h. Upon cooling, the mixture was filtered and the solvent was evaporated. The residue was taken up in chloroform (90 mL) and was washed with water. After drying (sodium sulfate), the solvent was evaporated to provide the crude 6-iodo-3,4-di-O-acetyl-D-glucal (3.13 g, quantitative): IR ($CHCl_3$) 1745, 1650, 1225 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.06 (s, 3H), 2.09 (s, 3H), 3.37 (m, 2H), 4.00 (m, 2H), 4.85 (m, 1H, J=7), 5.25 (m, 1H), 6.45 (dd, 1H, J=1,7).

To the iodide (5.85 g, 22.60 mmol) in dry benzene (220 mL) under nitrogen was added tri-n-butyltin hydride (14.28 g, 49.70 mmol) and a catalytic amount of azobisisobutyronitrile. After refluxing for

40 min, the solution was concentrated and the residue was taken up in ether. This ethereal solution was washed with water and the aqueous phase was extracted with ether (1 x). A brine wash of the organic portion, followed by drying (sodium sulfate), and solvent evaporation gave a residue which was flash chromatographed (50mm x 6" SiO_2, 5-15% ethyl acetate/hexane gradient) to furnish 4.50 g (92%) of 52 as a colorless liquid: IR (film) 1740, 1645, 1230 cm^{-1}; ^1H NMR δ 1.28 (d, 3H, J=7), 2.03 (s, 3H), 2.07 (s, 3H), 4.15 (broad p, 1H, J=7), 4.75 (dd, 1H, J=3,6), 4.95 (dd, 1H, J=3,6), 5.25 (m, 1H), 6.40 (dd, 1H, J=1,6).

(4S,5R)-4-Acetoxy-5-hydroxy-2-hexen-1-al (48)

Compound 52 (1.20 g, 5.50 mmol) was stirred with mercuric sulfate (0.055 g, 0.18 mmol) in dioxane (3.5 mL), acetone (4.5 mL), and 0.50 M sulphuric acid (22 mL). After 3 h at room temperature, the reaction was quenched with excess barium carbonate. The solvent was evaporated and the residue was flash chromatographed (40mm x 6" SiO_2, 50% ethyl acetate/hexane) to provide 0.747 g (79%) of 48 as a colorless liquid, which was contaminated with 0.132 g (14%) of the more mobile 5-acetoxy-4-hydroxy-2-hexen-1-al. Compound 48: IR ($CDCl_3$) 3470 broad, 1740, 1690 1225 cm^{-1}; $[\alpha]_D^{23}$ +5.2 (c 8.0, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.25 (d, 3H, J=7), 2.18 (s, 3H), 4.06 (dq, 1H, J=4,7), 5.33 (ddd, 1H, J=1,4,6), 6.26 (ddd, 1H, J=1,7,15), 6.82 (dd, 1H, J=6,15), 9.56 (d, 1H, J=7); MS m/z 171 (M-1), 43. 5-acetoxy isomer: IR ($CHCl_3$) 3470 broad, 1740, 1690, 1225 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.25 (d, 3H, J=7), 2.09 (s, 3H), 4.52 (m, 1H), 5.10 (m, 1H), 6.26 (ddd, 1H, J=1,7,15), 6.82 (dd, 1H, J=6,15), 9.56 (d, 1H, J=7); MS m/z 171 (M-1), 43.

(7S,8R)-8-Acetoxy-7-hydroxy-3,5-nonadien-2-one (54)

A solution of triphenylphosphineacetylmethylene (0.203 g, 0.640 mmol) and 48 (0.100 g, 0.580 mmol) in dry benzene (4 mL) was refluxed for 5 h. Upon solvent evaporation, the residue was taken up in ether and the triphenylphosphine oxide was filtered off. Evaporation of the ether, followed by flash chromatography (30mm x 5.5" SiO_2, 60% ethyl acetate/30% hexane/10% methylene chloride), provided 0.125 g (95%) of 54 (R_f 0.35) and 50 (R_f 0.27) in a ratio of 3.5:1, respectively. Compound 50: IR ($CHCl_3$) 3490 broad, 1730, 1670 cm^{-1}; $[\alpha]_D^{23}$ +43.1 (c 2.0, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.17 (d, 3H, J=7), 2.11 (s, 3H), 2.28 (s, 3H), 3.95 (m, 1H), 5.24 (dd, 1H, J=4,6), 5.8-6.6 (m, 3H), 7.09 (dd, 1H, J=10,16); UV (EtOH) λ_{max} 266.2 nm; MS m/z 213 (M+1), 195, 126, 43; exact mass m/z 126.069 (calcd for $C_7H_{10}O_2$: 126.068). Compound 54: IR ($CHCl_3$) 3490 broad, 1730, 1670 cm^{-1}; $[\alpha]_D^{23}$ +5.6 (c 6.9, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.22 (d, 3H, J=7), 2.07 (s, 3H), 2.28 (s, 3H), 4.35 (broad q, 1H, J=4), 4.96 (dq, 1H, J=4,7), 5.8-6.6 (m, 3H), 7.09 (dd, 1H, J=10,16); UV (EtOH) λ_{max} 268.2 nm; MS m/z 213 (M+1), 195, 126, 43; exact mass m/z 126.069 (calcd for $C_7H_{10}O_2$: 126.068.

Isomerization of 50 to 54.

Isomer 50 (7.840 g, 0.037 mmol) in dimethylformamide (240 mL) was heated to 90°C for 3 h with triethylamine (1.880 g, 0.018 mmol) under nitrogen. The reaction mixture was allowed to cool and added to water (400 mL), which was saturated with sodium chloride. Extraction into ether (6 x 150 mL), drying (sodium sulfate), and removal of solvent

provided an oil, which was flash chromatographed (270 g SiO_2, 50% ethyl acetate/30% hexane/10% methylene chloride) to give 7.213 g (92%) of 54:50 (3:1).

(7S,8R)-8-Acetoxy-7-acryloxy-3,5-nonadiene-2-one (58).

To the alcohol 54 (0.049 g, 0.230 mmol) and diisopropylethylamine (0.061 g, 0.460 mmol) in methylene chloride (3 mL) at -78°C under argon was added acryloyl chloride (0.036 g, 0.410 mmol). The reaction mixture was allowed to warm slowly to room temperature over 6 h. TLC analysis revealed that 54 remained, so the mixture was cooled again and diisopropylethyl amine (0.033 g, 0.230 mmol) and acryloyl chloride (0.018 g, 0.200 mmol) were added. After 3 h, the reaction mixture was poured into water (5 mL) and ether (20 mL). The organic phase was separated, washed with brine, and dried (sodium sulfate). The solvent was evaporated and the residue was flash chromatographed (10mm x 4" SiO_2, 50% ethyl acetate/hexane) to provide 0.0619 (100%) of 58 as an oil: IR ($CHCl_3$) 1730, 1685, 1665, 1230, 1170 cm^{-1}; $[\alpha]_D^{23}$ -32.7 (c 5.0, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.27 (d, 3H, J=7), 2.05 (s, 3H), 2.29 (s, 3H), 5.12 (dq, 1H, J=4,7), 5.52 (dd, 1H, J=4,6), 5.7-7.2 (m, 6H); MS m/z 220, 205, 180, 55, 43; exact mass m/z 180.079 (calcd for $C_{10}H_{12}O_3$: 180.079.

(2R,3S)-2-Acetoxy-3-acryloxy-8-(1-t-butyldimethylsiloxyethyl)-4,6-nonadiene (59).

To a solution of ketone 58 (0.251 g, 0.943 mmol) and cerium(III) chloride (0.351 g, 0.943 mmol) in methanol (25 mL) at -5°C under argon

was added sodium borohydride (0.084 g, 3.000 mmol). After 1.5 h, the reaction mixture was diluted with ether and washed with water. The aqueous phase was extracted with ether (3 x) and the combined organic portions were dried (sodium sulfate). Solvent evaporation supplied crude (2R,3S)-2-acetoxy-3-acryloxy-4,6-nonadiene-8-ol as an oil (0.252 g, quantitative): IR ($CHCl_3$) 3475 broad, 1730, 1250 cm^{-1}; ^1H NMR δ 1.20 and 1.22 (two d, 3H, J=7), 1.35 (d, 3H, J=8), 2.02 (s, 3H), 4.30 (m, 1H) 4.7-5.2 (m, 2H), 5.2-6.5 (m, 7H); MS m/z 164, 61, 43; exact mass m/z 164.084 (calcd for $C_{10}H_{12}O_2$: 164.084).

A solution of the alcohol (0.310 g, 1.157 mmol) in methylene chloride (10 mL) at 0°C under argon was treated with 2,6-lutidine (0.337 mL, 2.893 mmol) and t-butyldimethylsilyl triflate (0.458 g, 1.735 mmol). After 10 min, a trace of the starting alcohol remained, so an additional portion of lutidine (0.040 mL) and triflate (0.046 g) was added. After 5 min, the reaction mixture was diluted with methylene chloride and was stirred with 50% potassium hydroxide (4 mL) for 10 min. The organic portion was further diluted with ether and was separated. It was washed sequentially with saturated aqueous sodium bicarbonate and brine. Upon drying (sodium sulfate), the solvent was evaporated and the oil was flash chromatographed (20mm x 6" SiO_2, 20% ethyl acetate/hexane) to give 0.402 g (90%) of 59 as a colorless oil: IR ($CHCl_3$) 1730, 1240 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.07 (s, 6H), 0.92 (s, 9H), 1.23 (two d, 3H, J=7), 1.51 (d, 3H, J=8), 2.05 (s, 3H), 4.35 (broad p, 1H, J=7), 5.10 (dq, 1H, J=5,8); MS m/z 382 (M^+), 325 (M-57), 310, 129, 43; exact mass m/z 382.219 (calcd for $C_{20}H_{34}O_5Si$: 382.218).

(3S,3aS,6S,7aS)-3-((1R)-Acetoxyethyl)-6-(1-t-butyldimethylsiloxyethyl)-3a,5,7,7a-tetrahydro-1(3H)-isobenzofuranone (60A), (3aS,6S,7aR)-isomer (60B), and (3aR,6R,7aS)-isomer (60C).

The trieneoate 59 (0.250 g, 0.654 mmol) in dry, degassed toluene (25 mL) with 2,6-di-t-butyl-4-methylphenol (0.010 g) was heated in a sealed tube at 210°C for 72 h. Upon cooling, the solvent was removed in vacuo and the residue was flash chromatographed (30mm x 7.5" SiO_2, 15% ethyl acetate/hexane) to afford 0.214 g (85%) of three isomers, 60A, 60B, 60C, in a ratio of 2.5:2.5:1. The most mobile isomer was 60A: IR ($CHCl_3$) 1785, 1735 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.05 (s, 6H), 0.85 (s, 9H), 1.12 and 1.15 (two d, 3H, J=7), 1.33 (d, 3H, J=6), 1.6-2.6 (m, 5H), 2.06 (s, 3H), 3.88 (m, 2H), 5.08 (dq, 1H, J=6, 7), 5.80 (m, 2H); MS m/z 348, 325 (m-57), 159, 73; exact mass m/z 325.148 (calcd for $C_{16}H_{25}O_5Si$: 325.147). Isomer 60B: IR ($CHCl_3$) 1785, 1735 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.03 (s, 6H), 0.85 (s, 9H), 1.16 and 1.18 (two d, 3H, J=7), 1.30 (d, 3H, J=7), 1.5-2.2 (m, 3H), 2.75 (m, 2H), 3.70 (dq, 1H, J=4,7), 4.12 (dd, 1H, J=5,10), 5.10 (dq, 1H, J=5, 7), 5.4-6.1 (m, 2H); MS m/z 348, 325 (M-57), 159, 73; exact mass m/z 325.147 (calcd for $C_{16}H_{25}O_5Si$: 325.147). The least mobile isomer was 60C: IR ($CHCl_3$) 1785 1735 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.04 (s, 6H), 0.88 (s, 9H), 1.14 (d, 3H, J=7), 1.30 (d, 3H, J=7), 1.6-2.2 (m, 3H), 2.02 (s, 3H), 2.72 (dt, 1H, J=5,9), 3.18 (m, 1H), 3.61 (dq, 1H, J=5,7), 4.43 (t, 1H, J=8), 4.92 (dq, 1H, J=7,8), 5.52 (ddd, 1H, J=2,4,10), 6.02 (broad dt, 1H, J=2,10); MS m/z 348, 325 (M-57), 159, 73; exact mass m/z 325.148 (calcd for $C_{16}H_{25}O_5Si$: 325.147).

Epimerization of 60A to 60B.

To a solution of 60A (0.690 g, 1.806 mmol) in dry tetrahydrofuran (10 mL) at -78°C under nitrogen was added a solution of lithium diisopropylamide (0.772 M, 1.445 mmol) in dry tetrahydrofuran (2 mL). The reaction mixture was left to warm to room temperature over 4 h. The reaction was quenched with saturated aqueous ammonium chloride and the organic material was extracted with ether (3 x). The combined ethereal layers were washed with brine and dried (sodium sulfate). After evaporation, flash chromatography (40mm x 6" SiO_2, 15% ethyl acetate/hexane) provided 0.540 g (78%) of 60B, accompanied by recovered 60A.

Epimerization of 60C to (3S,3aR,6R,7aR)-3-((1R)-Acetoxyethyl)-6-(1-t-butyldimethylsiloxyethyl)-3a,6,7,7a-tetrahydro-1(3H)-isobenzofuranone (60D).

To a solution of 60C (0.022 g, 0.052 mmol) in dry tetrahydrofuran (2 mL) at -60°C under argon was added a solution of lithium diisopropylamide (0.120 M, 0.042 mmol) in dry tetrahydrofuran (0.35 mL). The reaction was allowed to warm at room temperature, and was stirred for 18 h. The mixture was quenched by pouring it into a mixture of ether and saturated aqueous ammonium chloride. The aqueous phase was extracted with ether (3 x) and the combined organic portions were washed with brine and dried (sodium sulfate). Solvent evaporation, followed by flash chromatography (12mm x 5" SiO_2, 25% ethyl acetate/hexane), yielded 0.016 g (73%) of recovered starting material and 0.005 g (22%) of the less mobile 60D: IR ($CHCl_3$) 1785, 1735 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.04 (s, 6H), 0.88 (s, 9H), 1.13 (d, 3H, J=6), 1.31 (d, 3H, J=7),

1.7-2.3 (m, 3H), 2.11 (s, 3H), 2.4-3.1 (m, 2H), 3.63 (p, 1H, J=6), 4.3 (m, 1H), 4.88 (t, 1H, J=10), 5.5 (broad d, 1H, J=10), 5.7-6.1 (broad d, 1H, J=10); MS m/z 325 (m-57), 159, 73; exact mass m/z 325.148 (calcd for $C_{16}H_{25}O_5Si$: 325.147).

(1S,2S,5S)-5-(1-t-Butyldimethylsiloxyethyl)-1-carbomethoxy-2-((1S,2R)-dihydroxypropyl)cyclohex-3-ene (62).

To a solution of 60A (0.023 g, 0.060 mmol) in MeOH (0.6 mL) at 0°C was added potassium carbonate (0.006 g, 0.044 mmol). After 1.5 h, the mixture was diluted with ethyl acetate and neutralized by adding water and 2 drops of 10% hydrochloric acid. The aqueous phase was separated and extracted with ethyl acetate. The organic portions were combined, washed with brine, and dried (sodium sulfate). The solvent was evaporated to give a residue, which was flash chromatographed (7mm x 7" SiO_2, 25% ethyl acetate/hexane) to afford 0.012 g (59%) of 61 as an oil and 0.005 (22%) of 62 as a solid. Compound 61: IR ($CHCl_3$) 3500 broad, 1730, 1360 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.05 (s, 6H), 0.88 (s, 9H), 1.15 (d, 3H, J=6), 1.30 (d, 3H, J=6), 1.7-2.3 (m, 3H), 2.05 (s, 3H), 2.65 (m, 1H), 2.95 (m, 1H), 3.65 (m, 1H), 3.70 (s, 3H), 5.0 (m, 1H), 5.5-6.0 (m, 2H); MS m/z 357, 325, 159. Compound 62: IR ($CHCl_3$) 3500 broad, 1730 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.05 (s, 6H), 0.89 (s, 9H), 1.17 (d, 3H, J=8), 1.23 (d, 3H, J=8), 1.7-2.3 (m, 5H), 2.72 (m, 1H), 3.02 (m, 1H), 3.30-3.85 (m, 3H), 3.68 (s, 3H), 5.30-6.05 (m, 2H); MS m/z 371 (M-1), 315 (M-57), 157; exact mass m/z 315.164 (calcd for $C_{15}H_{27}O_5Si$: 315.163).

(3R,4S,4aS,7S,8aS)-7-(1-t-Butyldimethylsiloxyethyl)-3,4,4a,7,8,8a-hexahydro-4-hydroxy-3-methyl-1H-2-benzopyran-1-one (63).

A solution of 62 (0.022 g, 0.059 mmol) in benzene (10 mL) and a catalytic amount of p-toluenesulfonic acid was stirred at room temperature for 15 h. The mixture was concentrated to one half of its original volume and then diluted with ether. The ethereal solution was washed with 10% aqueous sodium bicarbonate and the aqueous portion was extracted with ether (3 x). The combined organic layers were washed with brine and dried (sodium sulfate). Solvent removal in vacuo gave 0.020 g (99%) of 63 as colorless crystals: dec 235°C; IR ($CHCl_3$) 3450, 1730, 1370, 1105 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.04 (s, 6H), 0.88 (s, 9H), 1.18 (d, 3H, J=6), 1.45 (d, 3H, J=7), 1.7-2.9 (m, 5H), 3.8 (m, 2H), 4.3 (m, 1H), 5.5-6.2 (m, 2H); MS m/z 341 (M+1), 296, 155, 65.

Methyl Xanthate (64).

The alcohol 63 (0.0105 g, 0.0290 mmol), imidazole (0.001 g, 0.014 mmol), 60% sodium hydride in oil (0.005 g, 0.125 mmol) in dry tetrahydrofuran (1 mL) were stirred at room temperature for 4.75 h. Carbon disulfide (0.440 g, 0.588 mmol) was added and the mixture was stirred an additional hour. Upon quenching the reaction with methyl iodide (0.052 g, 0.071 mmol) over a 1 h period, the mixture was diluted with ether and the combined organic portions were washed with brine and dried (sodium sulfate). Solvent evaporation gave a residue which was flash chromatographed (5mm x 2" SiO_2, 15% - 35% ethyl

acetate/hexane gradient) to furnish 0.002 g (18%) of 64 as an oil: IR ($CHCl_3$) 1708 broad, 1365, 1070 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.04 (s, 6H, 0.88 (s, 9H), 1.23 (d, 3H, J=7), 1.55 (d, 3H, J=7), 1.9-3.2 (m, 7H), 3.48 and 3.62 (two s, 3H), 3.70 (m, 1H), 5.50-6.25 (m, 2H); MS m/z 430 (M^+), 373 (M-57), 159; exact mass m/z 373.094 (calcd for $C_{16}H_{25}O_4S_2Si$: 373.096).

(3S,3aS,6S,7aR)-6-(1-t-Butyldimethylsiloxyethyl)-3-((1R)-hydroxyethyl)-3a,6,7,7a-tetrahydro-1(3H)-isobenzofuranone (65).

Adduct 60B (0.076 g, 0.199 mol) and potassium carbonate (0.034 g, 0.250 mol) in methanol (4 mL) at 0°C were stirred for 2.5 h. The reaction mixture was poured into saturated aqueous ammonium chloride and extracted with ether (3 x). The combined organic portions were washed with brine, dried (sodium sulfate), and concentrated in vacuo. The residue was flash chromatographed (15mm x 6" SiO_2, 35% ethyl acetate/hexane) to yield 0.052 g (78%) of 65 as an oil, together with a small quantity of the dihydroxy methyl ester. Compound 65: IR ($CHCl_3$) 3400 broad, 1765 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.05 (s, 6H), 0.88 (s, 9H) 1.09 (d, 3H, J=7), 1.23 (d, 3H, J=7), 1.7-2.3 (m, 4H), 2.6-3.2 (m, 2H), 3.5-4.4 (m, 2H), 5.6-6.1 (m, 2H); MS m/z 296, 283 (M-57), 159, 75; exact mass m/z 283.137 (calcd for $C_{14}H_{19}O_4Si$: 283.136).

(3S,3aS,6S,7aR)-3-Acetyl-6-(1-t-butyldimethylsiloxyethyl)-3a,6,7,-7a-tetrahydro-1(3H)-isobenzofuranone (66).

To a solution of the alcohol 65 (0.055 g, 0.161 mmol) in methylene chloride (10 mL) was added pyridinium chlorochromate (0.208 g,

0.966 mmol) over a 6 h period. After stirring for 19 h, the mixture was diluted with ether (6 x) and filtered through Celite (20mm x 4"). Solvent evaporation gave a residue which was flash chromatographed (10mm x 6" SiO_2, 15-25% ethyl acetate/hexane gradient) to provide 0.046 g (85%) of 66 as an oil: IR (film) 1785, 1720 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.05 (s, 6H), 0.88 (s, 9H), 1.13 and 1.15 (two d, 3H, J=6), 1.3-2.3 (m, 3H), 2.32 (s, 3H), 2.8 (m, 2H), 3.8 (m, 1H), 4.38 (d, 1H, J=9), 5.6-6.1 (m, 2H); MS m/z 281 (M-57), 159, 63; exact mass m/z 281.121 (calcd for $C_{14}H_{21}O_4Si$: 281.121).

(3S,3aR,6R,7aS)-3-Acetyl-6-(1-t-butyldimethylsiloxyethyl)-3a,6,7,7a-tetrahydro-1(3H)-isobenzofuranone (67).

Compound 60C (0.009 g, 0.023 mmol) and potassium carbonate (0.004 g, 0.027 mmol) in methanol (1 mL) was stirred at 0°C and allowed to warm to room temperature over 6 h. The reaction mixture was diluted with ether and washed with saturated aqueous ammonium chloride. The aqueous phase was extracted with ether (3 x), and the combined organic portions were washed with brine, and dried (sodium sulfate). The solvent was removed in vacuo to provide 0.005 g (64%) of crude (3S,3aR,6R,7aS)-6-(1-t-butyldimethylsiloxyethyl)-3-((1R)-hydroxyethyl)-3a,6,7,7a-tetrahydro-1(3H)-isobenzofuranone: IR ($CHCl_3$) 3400 broad, 1770, 1365, 1090 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.02 (s, 3H), 0.05 (s, 3H), 0.90 (s, 9H), 1.22 (d, 3H, J=7), 1.35 (d, 3H, J=6), 1.5-2.2 (m, 3H), 2.78 (complex t, 1H, J=9), 3.20 (m, 1H), 3.5-4.3 (m, 3H), 5.7-6.2 (m, 2H); MS m/z 296, 283 (M-57), 159; exact mass m/z 283.137 (calcd for $C_{14}H_{19}O_4Si$: 283.136).

To a solution of this alcohol (0.005 g, 0.015 mmol) in methylene chloride (1 mL) was added pyridinium chlorochromate (0.021 g, 0.100 mmol). After stirring 19 h, the mixture was diluted with ether (5 x) and was filtered through Celite. Solvent evaporation provided 0.005 g (95%) of crude 67: IR (film) 1785, 1720 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.06 (s 6H), 0.89 (s, 9H), 1.08 (d, 3H, J=7), 1.3-2.3 (m, 3H), 2.15 (s, 3H), 2.15 (m, 1H), 2.75 (m, 1H), 3.37 (dddd, 1H, J=1,2,10,10), 3.78 (m, 1H, J=7), 4.92 (d, 1H, J=10), 5.65 (ddd, 1H, J=2,4,10), 5.9 (broad d, 1H, J=10); MS m/z 281 (M-57), 159, 63; exact mass m/z 281.121 (calcd for $C_{14}H_{21}O_4Si$: 281.121).

Epimerization of 67 to (3R,3aR,6R,7aS)-3-Acetyl-6-(1-t-butyldimethylsiloxyethyl)-3a,6,7,7a-tetrahydro-1(3H)-isobenzofuranone (68).

To a solution of 67 (0.004 g, 0.012 mmol) in methanol (2 mL) was added at room temperature a 0.460 M sodium methoxide/methanol solution (0.028 mL, 0.26 mmol) under argon. After 7 h, the mixture was warmed to 60°C for 6 h. The reaction mixture was cooled and diluted with ether. The solution was washed with saturated aqueous ammonium chloride and the aqueous layer was extracted with ether (5 x). The combined organics were washed with brine and dried (sodium sulfate). Removal of solvent in vacuo, followed by chromatography (5mm x 2" SiO_2, 50% ethyl acetate/hexane), yielded 67 and its isomer 68, in a ratio of 1:2, respectively. Compound 68: IR ($CHCl_3$) 1785, 1720 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.05 (s, 6H), 0.88 (s, 9H), 1.13 and 1.15 (two d, 3H, J=6), 1.3-2.3 (m, 3H), 2.32 (s, 3H), 2.8 (m, 2H), 3.8 (m, 1H), 4.38 (d, 1H, J=9), 5.6-6.1 (m, 2H).

(3S,3aS,6S,7aR)-3-Acetyl-6-(1-hydroxyethyl)-3a,6,7,7a-tetrahydro-1-(3H)-isobenzofuranone (69).

1. Amalgamated zinc (10.00 g) and chromic chloride (6.00 g) were stirred in saturated aqueous ammonium chloride (15 mL) until a dark blue color persisted. This chromous chloride solution (5 mL) was added to a solution of 66 (0.002, 0.006 mmol) in acetone (1 mL) and the blue solution was stirred for 4 h at 23°C, then at 40°C for 18 h. Acetone was evaporated and the aqueous phase was extracted with ether (5 x). The solvent was removed in vacuo and the residue was chromatographed (5mm x 1.5" SiO_2, 60% ethyl acetate/hexane) to give 0.001 g (89%) as an oil.

2. A solution of 66 (0.004 g, 0.015 mmol) in tetrahydrofuran (0.5 mL) was stirred for 18 h with acetic acid (1.5 mL) and water (0.5 mL). The reaction mixture was warmed to 40°C for 4 h, then cooled and extracted with ether (5 x). The organic portion was washed with brine, dried (sodium sulfate), and concentrated to furnish quantitatively the crude alcohol 69: IR ($CHCl_3$) 3400 broad, 1785 1720 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.23 and 1.26 (two d, 3H, J=6), 1.3-2.3 (m, 3H), 2.32 (s, 3H), 2.5-3.2 (m, 2H), 3.70 (m, 1H), 4.43 and 4.47 (two d, 1H, J=7 and 9), 5.7-6.2 (m, 2H); MS m/z 224 (M^+); exact mass m/z 224.105 (calcd for $C_{12}H_{16}O_4$: 224.104).

(1R,5S,8S)-4-Methyl-3-oxa-2-oxo-8-(2-oxopropyl)bicyclo[3.3.1]-non-6-ene (71).

The keto lactone 66 (0.004 g, 0.012 mmol) and freshly purified zinc dust (0.10 g) were refluxed in glacial acetic acid (1.0 mL) for 17 h. After cooling, the mixture was filtered and the filtrate was diluted with ether and washed with brine. The solvent was dried (sodium sulfate) and evaporated. Chromatography (7mm x 2" SiO_2, 35% ethyl acetate/hexane) furnished 0.001g (40%) of 71: IR ($CHCl_3$) 1720 1355 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.2-1.7 (m, 5H), 1.9-3.2 (m, 5H), 2.19 (s, 3H), 4.5 (m, 1H), 5.3-5.9 (m, 2H); MS m/z 208 (M^+), 195; exact mass m/z 208.110 (calcd for $C_{12}H_{16}O_3$: 208.110).

1,5-Anhydro-3,4-di-O-acetyl-L-rhamno-hex-1-enitol (3,4-Diacetoxy-L-rhamnal, 72)

To a solution of L-(+)-rhamnose monohydrate 73 (5.00 g, 27.40 mmol) in dry pyridine (25 mL) was added at 0°C freshly distilled acetic anhydride (25 mL). After 48 h at room temperature, the solution was evaporated and the syrup was taken up in ice and methylene chloride. The aqueous layer was separated and extracted with methylene chloride (2 x). The combined extracts were washed several times alternately with dilute sulfuric acid and saturated aqueous potassium hydrogen carbonate. The organic phase was dried with calcium chloride, decanted and evaporated to yield 9.30 g (94%) of 1,2,3,4-tetra-O-acetyl-L-rhamnose as a yellow syrup: ^1H NMR ($CDCl_3$) δ 1.18 (d, 3H, J=7), 1.99 (s, 3H), 2.04 (s, 3H), 2.14 (s, 3H), 2.16 (s, 3H), 3.9 (m, 1H),

4.95-5.20 (m, 3H), 5.97 (broad s, 1H).

The tetraacetate (9.50 g, 27.00 mmol) was dissolved in a mixture of glacial acetic acid (3 mL) and acetic anhydride (3 mL) at 0°C, and a 0°C solution of 28% hydrobromic acid in acetic acid (19 mL) was added. The solution was kept at 16°C for 2.5 h, during which time it turned red. This reaction mixture was added to a solution prepared in the following way. In a flask, equipped with a mechanical stirrer and a thermometer, sodium acetate trihydrate (25.0 g) was dissolved in 50% acetic acid (60 mL). After cooling to -10°C, a solution of zinc dust (18.0 g) and cupric sulfate pentahydrate (1.8 g) in water (15.5 mL) was added with vigorous stirring. After the blue color had disappeared, the solution of pyranosyl bromide was added over 1 h, maintaining an internal temperature of -10 to -5°C. The mixture was stirred an additional 2.5 h and filtered. The filter was rinsed with 50% acetic acid which had been cooled to -10°C. Crushed ice (50 g) was added to the filtrate and the mixture was extracted with chloroform (3 x). The combined extracts were washed with water (0°C), and then with cold saturated aqueous potassium carbonate until the acetic acid was completely removed. The solution was dried (calcium chloride), decanted, and evaporated (bath temperature of 40°C). The residue was flash chromatographed (50mm x 3" SiO_2, 20% ethyl acetate/hexane) to provide 5.30 g (80%) of 77 as a colorless oil: ^1H NMR ($CDCl_3$) δ 1.28 (d, 3H, J=7), 2.03 (s, 3H), 2.07 (s, 3H), 4.15 (broad p, 1H, J=7), 4.75 (dd, 1H, J=3,6), 4.95 (dd, 1H, J=3,6), 5.25 (m, 1H), 6.40 (dd, 1H, J=1,6).

(3R,3aS,4S,5R,6R,7aR)-3-((1S)-Acetoxyethyl)-6-(1-t-butyldimethylsiloxyethyl)-4,5-dihydroxy-3a,4,5,6,7,7a-hexahydro-1(3H)-isobenzofuranone (76A) and (4R,5S)-isomer (76B).

To a solution of 75A (0.035 g, 0.090 mmol) in 0.1 mL of acetone and 0.4 mL of water under argon was added 4-methylmorpholine-N-oxide monohydrate (0.062 g, 0.450 mmol), followed by a 2.5% solution of osmium tetroxide in t-butanol (0.020 mL). The reaction mixture was stirred for 20 h, and then another 0.062 g of the N-oxide was added. After 24 h, the reaction was quenched by addition of a slurry of Florisil (0.018 g) and sodium hydrosulfite (0.009 g) in water, and the mixture was stirred for 10 min. Upon filtration and washing of the filter cake with ether, the aqueous portion was saturated with ammonium chloride and extracted with ether (5 x). The combined organic layers were washed with brine and dried (sodium sulfate). The solvent was evaporated to give a residue (0.044 g), which was flash chromatographed (10mm x 5.5" SiO_2, 50% ethyl acetate/hexane), providing two isomeric diols in a ratio of 1:1. More mobile isomer 76A: IR ($CHCl_3$) 3450 broad, 2950, 1780, 1730, 1370 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.10 (s, 6H), 0.90 (s, 9H), 1.30 (m, 6H), 1.5-2.5 (m, 4H), 2.07 and 2.10 (two s, 3H), 3.0 (m, 1H), 3.7-5.3 (m, 5H). Less mobile isomer 76B: IR ($CHCl_3$) 3550 broad, 2950, 1785, 1725, 1375, cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.10 (s, 6H), 0.90 (s, 9H), 1.26 (d, 3H), J=8), 1.34 (d, 3H, J=8), 1.5-3.2 (m, 5H), 2.10 (s, 3H), 3.8-4.4 (m, 4H), 5.18 (dq, 1H, J=4,8).

(3R,3aS,4S,5R,6R,7aR)-3-((1S)-Acetoxyethyl-6-(1-t-butyldimethylsiloxyethyl)-4,5-dihydroxy-3a,4,5,6,7,7a-hexahydro-1(3H)-isobenzofuranone Cyclohexylidene Ketal (77) and (3R,3aS,4S,7R,8aR,9R)-3-((1S)-Acetoxyethyl)-9-t-butyldimethylsiloxy-6-methyl-1,3,3a,4,5,7,8,8a-octahydro-4,7-methanofuro[3,4-c]oxepin-1-one (78).

The diol 76A (0.008 g, 0.020 mmol) in 1,1-dimethoxycyclohexane (1 mL) containing one crystal of camphorsulfonic acid was stirred for 1.5 h at 25°C. The reaction was judged incomplete by TLC analysis, so another crystal of the acid was added and the mixture was stirred an additional 1.5 h. The reaction mixture was then diluted with ether and washed with 50% aqueous sodium bicarbonate and water. The combined aqueous phases were extracted with ether (2 x). The ethereal layers were washed with brine and dried (sodium sulfate). Removal of the solvent (30°C/10 mm), followed by flash chromatography (7 mm x 2" SiO_2, 10-20% ethyl acetate/hexane gradient), furnished 0.003 g (30%) of 77 and 0.007 (70%) of 78. Compound 77: IR ($CHCl_3$) 2950, 1780, 1735, 1370, 1110 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.02 (s, 6H), 0.89 (s, 9H), 1.1-1.4 (m, 6H), 1.55 (m, 10H), 2.07 (s, 3H), 3.1-3.7 (m, 3H), 4.30 (m, 1H), 5.13 (m, 1H); MS m/z 497 (M+1), 496 (M^+), 453, 439; exact mass m/z 496.289 (calcd for $C_{26}H_{44}O_7Si$: 496.286). Compound 78: IR ($CHCl_3$) 2950, 1780, 1735, 1365, 1100 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.02 (s, 6H), 0.89 (s, 9H), 1.25 (d, 3H, J=7), 1.34 (d, 3H, J=8), 1.5-3.2 (m, 5H), 2.10 (s, 3H), 3.8-4.5 (m, 4H), 5.18 (dq, 1H, J=4,6); MS m/z 341 (M-57), 281, 159, 43; exact mass m/z 341.142 (calcd for $C_{16}H_{25}O_6Si$: 341.142).

(3R,3aS,4R,5S,6R,7aR)-3-((1S)-Acetoxyethyl-6-(1-t-butyldimethylsiloxyethyl)-4,5-dihydroxy-3a,4,5,6,7,7a-hexahydro-1(3H)-isobenzofuranone Cyclohexylidene Ketal (79).

The diol 76B (0.009 g, 0.020 mmol) and one crystal of camphorsulfonic acid in 1,1-dimethoxycyclohexane (2 mL) were stirred 1.5 h at 25 C. The reaction was worked up as for 77. Solvent evaporation (30°C/10 mm) gave 0.009 g (90%) of 79 as a foam: IR ($CHCl_3$) 2950 1780, 1730, 1360, 1090 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.08 (s, 6H), 0.90 (s, 9H), 1.25 (m, 6H), 1.60 (m, 10H), 1.6-2.4 (m, 3H), 2.08 (s, 3H), 3.1-3.7 (m, 2H), 3.9-4.3 (m, 4H), 5.19 (dq, 1H, J=5,6); MS m/z 497 (M+1), 496 (M^+), 439; exact mass m/z 496.288 (calcd for $C_{26}H_{44}O_7Si$: 496.286).

(3R,3aS,4R,5S,6R,7aS)-3-((1S)-Acetoxyethyl-6-(1-t-butyldimethylsiloxyethyl)-4,5-dihydroxy-3a,4,5,6,7,7a-hexahydro-1(3H)-isobenzofuranone (80).

To 75B (1.22 g, 3.19 mmol) in 20 mL of tetrahydrofuran-water (3:1) was added N-methylmorpholine-N-oxide (1.20 g, 9.00 mmol) and a 2.5% solution of osmium tetroxide in t-butanol (0.50 mL). After stirring for 40 h under argon, the reaction mixture was quenched by adding a slurry of sodium dithionite (4.0 g) and Florisil (30.0 g) in water, and the mixture was stirred for 10 min. After filtration of the solids, the filtrate was saturated with ammonium chloride and extracted with ethyl acetate (4 x). The combined organic layers were washed with brine, dried (sodium sulfate), and evaporated to furnish a foam

1.20 g (90%) of 80 as a foam: IR ($CHCl_3$) 3570 broad, 3450, 2960, 1740, 1380 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.11 (s, 6H), 0.90 (s, 9H), 1.25 (m, 6H), 1.5-2.3 (m, 3H), 2.05 and 2.07 (two s, 3H), 2.4-3.3 (m, 2H), 3.6-4.4 (m, 4H), 5.1 (m, 1H); MS m/z 359 (M-57), 299, 281; exact mass m/z 359.155 (calcd for $C_{16}H_{27}O_7Si$: 359.153).

(3R,3aS,4R,5S,6R,7aS)-3-((1S)-Acetoxyethyl)-6-(1-t-butyldimethylsiloxyethyl)-4,5-dihydroxy-3a,4,5,6,7,7a-hexahydro-1(3H)-isobenzofuranone Cyclohexylidene Ketal (81).

The diol 80 (0.011 g, 0.026 mmol) was stirred with 1, 1-dimethoxycyclohexane (2 mL) and camphorsulfonic acid (0.002 g, 0.008 mmol) for 8.5 h. The reaction mixture was diluted with ether and washed sequentially with 50% aqueous sodium bicarbonate and water. The aqueous layers were extracted with ether (3 x) and the combined organic layers washed with brine. Drying (sodium sulfate) and solvent evaporation (40°C/10 mm), yielded a single product, as judged by TLC, to give 0.012 g (96%) of 81 as a foam: IR ($CHCl_3$) 2950, 1775, 1740, 1370, 1100 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.04 (s, 3H), 0.07 (s, 3H), 0.88 (s, 9H), 1.0-1.8 (m, 12H), 1.21 and 1.24 (two d, 3H, J=6), 1.28 (d, 3H, J=7), 1.85-2.17 (two m, 1H), 2.04 (two s, 3H), 2.44 (m, 1H, J=2,9), 2.90 (q, 1H, J=9), 3.88-4.01 (m, 1H), 4.18 and 4.34 (two dd, 1H, J=7,8), 4.39 (dd, 1H, J=2,4), 5.12 (dq, 1H, J=4,7); MS m/z 496 (M^+), 453; exact mass m/z 496.289 (calcd for $C_{26}H_{44}O_7Si$: 496.286).

Epimerization of 79 to 81.

A solution of 79 (0.010 g, 0.019 mmol) in dry tetrahydrofuran (2 mL) was added at -78°C to a solution of 0.6 equivalents of lithium diisopropylamide in dry tetrahydrofuran (2 mL). After 10 min, the reaction was warmed to room temperature and was stirred for 12 h. The reaction was quenched by adding the mixture to water (10 mL) and ether (10 mL). The aqueous portion was extracted with ether and the ethereal layers were washed with brine and dried (sodium sulfate). Removal of solvent in vacuo gave an oil, which was flash chromatographed (7mm x 3" SiO_2, 10% ethyl acetate/hexane) to provide the more mobile 79 and the less mobile 81 in a ratio of 1:3.

(3R,3aR,4S,5R,6S,7aR)-3-((1S)-Acetoxyethyl-6-(1-t-butyldimethylsiloxyethyl)-4,5-dihydroxy-3a,4,5,6,7,7a-hexahydro-1(3H)-isobenzofuranone Cyclohexylidene Ketal (83).

To a solution of 75C (0.690 g, 1.800 mmol) in tetrahydrofuran (5 mL) was added a solution of N-methylmorpholine-N-oxide (1.20 g, 9.00 mmol) in water (5 mL) and 2.5% osmium tetroxide in t-butanol (0.200 mL). The mixture was stirred for 40 h at room temperature. Reduction of the osmate esters and extractive workup as previously described afforded, after flash chromatography, 0.350 g (40%) of 82 as a colorless foam. The foam was taken up in 1,1-dimethoxycyclohexane (7 mL) and stirred for 5 h with camphorsulfonic acid (0.50 equivalents). The reaction mixture was diluted with ether (10 mL) and washed with 50% aqueous sodium bicarbonate and water. The aqueous layers were

extracted with ether (3 x) and the combined organic layers were washed with brine, dried (sodium sulfate), and concentrated (40°C/10 mm). The residue was flash chromatographed (30mm x 5" SiO_2, 15% ethyl acetate/hexane) to give 0.625 (70%) of a colorless foam 83, which was found to be a single siloxyethyl epimer: IR ($CHCl_3$) 1775, 1740, 1370 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.05 (s, 3H), 0.06 (s, 3H), 0.89 (s, 9H), 1.17 (d, 3H, J=6), 1.2-1.8 (m, 12H), 1.41 (d, 3H, J=6), 1.98 (ddd, 1H, J=3,9,11), 2.03 (s, 3H), 2.59 (ddd, 1H, J=5,9,9), 2.99 (q, 1H, J=9), 3.99 (m, 2H), 4.15 (t, 1H, J=8), 4.42 (dd, 1H, J=5,7), 5.28 (dq, 1H, J=6,7); MS m/z 496 (M^+), 453, 439; exact mass m/z 496.289 (calcd for $C_{26}H_{44}O_7Si$: 496.286).

(3R,3aS,4R,5S,6R,7aS)-3-Acetyl-6-(1-t-butyldimethylsiloxyethyl)-4,5-dihydroxy-3a,4,5,6,7,7a-hexahydro-1-(3H)-isobenzofuranone Cyclohexylidene Ketal (84).

To a solution of impure acetate 81 (0.242 g, 0.488 mmol) in methanol (15 mL) at -5 to 0°C was added potassium carbonate (0.084 g, 0.610 mmol), and the reaction mixture was allowed to slowly warm to 25°C. After 6 h, the mixture was diluted with ether and neutralized with saturated aqueous ammonium chloride. The aqueous phase was extracted with ether (3 x). The combined organic portions were washed with brine and dried (sodium sulfate). Solvent was removed in vacuo and the residue was flash chromatographed (20mm x 6" SiO_2, 25% ethyl acetate/hexane) to afford (3R,3aS,4R,5S,6R,7aS)-6-(1-t-butyldimethylsiloxyethyl)-4,5-dihydroxy-3a,4,5,6,7,7a-hexahydro-3-((1S)-hydroxyethyl)-1(3H)-isobenzofuranone 0.165 g (72%) as a colorless foam, and a less mobile isomeric alcohol

(0.036 g, 16%). More mobile compound: IR ($CHCl_3$) 3450 broad, 2950, 1770, 1100 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.06 (s, 6H), 0.88 (s, 9H), 1.20 (d, 3H, J=7), 1.24 (d, 3H, J=7), 1.58 (m, 10H), 1.6-2.2 (m, 3H), 2.48 (broad ddt, 1H, J=1,10,10), 3.05 (broad dd, 1H, J=10,10), 3.8-4.4 (m, 4H); MS m/z 454 (M^+), 397 (M-57), 299; exact mass m/z 454.275 (calcd for $C_{24}H_{42}O_6Si$: 454.275). Less mobile compound: IR ($CHCl_3$) 3500 broad, 2950, 1775, 1060 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.08 (s, 6H), 0.90 (s, 9H), 1.1-1.4 (m, 6H), 1.6 (m, 10H), 1.8-2.8 (m, 4H), 2.98 (broad t, 1H, J=9), 3.8-4.4 (m, 4H); MS m/z 454 (M^+), 397 (M-57), 299, 255, 207; exact mass m/z 454.275 (calcd for $C_{24}H_{42}O_6Si$: 454.275).

A solution of the major, more mobile alcohol (0.160 g, 0.350 mmol) in methylene chloride (30 mL) was stirred for 4 h with pyridinium chlorochromate (0.379 g, 1.700 mmol). The reaction mixture was diluted with ether (5 x) decanted, and filtered through Celite (40mm x 4.5"). The solvent was evaporated and the residue was flash chromatographed (30mm x 4" SiO_2, 5% ether/methylene chloride) to provide 0.145 g (92%) of 84 as a foam: IR ($CHCl_3$) 2950, 1785, 1725, 1370, 1100 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.06 (s, 6H), 0.88 (s, 9H), 1.18 (d, 3H, J=6), 1.2-1.9 (m, 13H), 2.26 (s, 3H), 2.1-3.1 (m, 2H), 3.8-4.5 (m, 3H), 4.81 (d, 1H, J=2); MS m/z 452 (M^+), 395 (M-57), 297; exact mass m/z 452.258 (calcd for $C_{24}H_{40}O_6Si$: 452.259).

(1S,2S,3R,4S,5R)-5-(1-t-Butyldimethylsiloxyethyl)-1-carbomethoxy-3,4-dihydroxy-2-(2-oxopropyl)cyclohexane Cyclohexylidene Ketal (86).

1. To a solution of copper bromide dimethyl sulfide complex (0.116

0.570 mmol) in dry tetrahydrofuran (2.5 mL) and dimethyl sulfide 2.5 mL) was added at 0°C a 1.50 M solution of methyl lithium in hexane (0.75 mL, 1.12 mmol), and the colorless solution was stirred for 15 min. A solution of keto lactone 84 (0.095 g, 0.210 mmol) in dry tetrahydrofuran (2 mL) was then added at 0°C. The reaction mixture became greenish-brown within 2 min, and stirring was continued for 0.8 h. The mixture was poured into saturated aqueous ammonium chloride and extracted with ether (4 x). The organic portions were washed with 2% aqueous sodium bisulfite, brine, and then dried (sodium sulfate). Silica gel was added to the organic solution and removed by filtration. The solution was concentrated to 10 mL and treated with diazomethane to afford, after chromatography (10mm x 4" SiO_2, 33% ethyl acetate/hexane), 0.036 g (37%) of 86 as an oil: IR ($CHCl_3$) 2960, 1730 broad, 1470, 1365, 1260, 1155, 1100 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.10 (s, 6H), 0.93 (s, 9H), 1.21 (d, 3H, J=7), 1.3-2.0 (m, 13H), 2.18 (s, 3H), 2.1-3.2 (m, 4H), 3.68 (s, 3H), 3.8-4.4 (m, 3H); MS m/z 468 (M^+), 425, 411 (M-57); exact mass m/z 468.293 (calcd for $C_{25}H_{44}O_6Si$: 468.291).

2. To a solution of keto lactone 84 (0.015 g, 0.033 mmol) in dry tetrahydrofuran (0.3 mL) was added a 0.10 M solution of samarium diiodide in dry tetrahydrofuran (0.68 mL, 0.07 mmol). Upon addition, the blue-green color immediately faded to yellow. A further 2.00 mL of the samarium diiodide solution was added and the blue-green color persisted for 0.5 h. This procedure was repeated twice more. After 2 h, a catalytic amount of ferric chloride was added and the mixture was stirred for 16 h. The resulting, brown mixture was poured into saturated aqueous ammonium chloride and extracted with

ether (3 x). The red, organic portions were washed with water, 2% aqueous sodium thiosulfate, water, and brine. The solution was dried (sodium sulfate) and the solvent was removed to furnish an oil, which was taken up in ether and treated with diazomethane. After 2h, the solvent was evaporated to supply 0.014 g (66%) of 86 as a crude oil, which was contaminated with 84 (ca. 10%).

(4aS,5R,6S,7R,8aS)-7-(1-t-Butyldimethylsiloxyethyl)-5,6-dihydroxy-3-methoxy-2-decalen-1-one Cyclohexylidene Ketal (88A) and (4aS,5R,6S,7R,8aS)-7-(1-t-Butyldimethylsiloxyethyl)-5,6-dihydroxy-1-methoxy-1-decalen-3-one Cyclohexylidene Ketal (88B).

To a solution of keto ester 86 (0.0060 g, 0.0120 mmol) in dry benzene (7 mL) was added a 0.25 M solution of potassium t-butoxide in t-butanol (0.50 mL, 0.12 mmol). After 30 min, the reaction mixture was diluted with ether and acidified to pH5. The aqueous phase was separated and extracted with ethyl acetate (3 x). The organic portions were washed with brine and dried (sodium sulfate). The solution was concentrated to 10 mL and treated with diazomethane. After 2h, the solvent was removed in vacuo to give a residue, which was chromatographed (7mm x 2" SiO_2, 10-20% ethyl acetate/hexane gradient) furnishing 0.0034 g (63%) of 88A and 88B (2.4:1). The more mobile compound 88A showed: IR ($CHCl_3$) 2960, 1645, 1610, 1455, 1380, 1090 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.07 (s, 6H), 0.88 (s, 9H), 1.19 (two d, 3H, J=7), 1.2-1.9 (m, 13H), 2.1-2.9 (m, 4H), 3.72 (s, 3H), 3.8-4.2 (m, 3H), 5.35 (broad s, 1H); MS m/z 450 (M^+), 435, 407, 393; exact mass m/z 450.281 (calcd for $C_{25}H_{42}O_5Si$: 450.280). The less mobile compound 88B showed: IR

($CHCl_3$) 2960, 1645, 1610, 1460, 1380, 1095, 890 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.06 (s, 6H), 0.89 (s, 9H), 1.2 (d, 3H), 1.3-3.0 (m, 17H), 3.71 (s, 3H), 3.9-4.3 (m, 3H), 5.35 (broad s, 1H); MS m/z 450 (M^+), 435, 407, 393; exact mass m/z 450.281 (calcd for $C_{25}H_{42}O_5Si$: 450.280).

(2R,3S,4R,4aS,12aS)-2-(1-t-Butyldimethylsiloxyethyl)-1,2,3,4,4a,12a-hexahydro-10-methoxy-3,4,11-trihydroxy-12(5H)-naphthacenone Cyclohexylidene Ketal (89).

To a solution of 34 (0.048 g, 0.250 mmol) in 2.5 mL of dry tetrahydrofuran at -78°C under nitrogen was added a 0.38 M solution of lithium diisopropylamide in dry tetrahydrofuran (1 mL, 0.38 mmol). The orange-red solution was stirred an additional 15 min before adding a solution of 88A (0.032 g, 0.071 mmol) in dry tetrahydrofuran (0.3 mL) over a 10 min period. The reaction was kept at -78°C for 10 min, then warmed to 26°C over 0.5 h. Quenching with saturated aqueous ammonium chloride gave a fluorescent yellow solution, which was extracted with ether (2 x). The combined organic solution was washed with water and brine, and dried (sodium sulfate). Upon solvent evaporation, the residue was flash chromatographed (10mm x 5" SiO_2, 85% methylene chloride/hexane) to give 89, along with the toluate dimer 38. The fluorescent material was again chromatographed, using a 50-75% methylene chloride/hexane gradient as the eluant, to furnish 0.012 g (32%) of 89 as a yellow oil: IR ($CHCl_3$) 3020, 2940, 1625, 1570, 1470, 1280, 1220, 700 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.04 (s, 6H), 0.86 (s, 9H), 1.4-1.8 (m, 10H), 2.9 (m, 2H), 3.8-4.3 (m),

6.7-7.5 (m); UV ($CHCl_3$) λ_{max} 269, 398 nm; MS m/z 567 (M+1), 566 (M^+), 509, 411, 241.

(2R,3S,4R,4aS,12aS)-11-Acetoxy-2-(1-t-butyldimethylsiloxyethyl-3, 4-dihydroxy-1,2,3,4,4a,12a-hexahydro-10-methoxy-12(5H)-naphthacenone Cyclohexylidene Ketal (90).

To a solution of 89 (0.0125 g, 0.0220 mmol) in dry methylene chloride (0.5 mL) at room temperature under argon was added triethyl amine (0.100 mL), acetic anhydride (0.100 mL), and 4-dimethylaminopyridine (0.001 g, 0.008 mmol), and the reaction was stirred for 3 h. Filtration through a plug of silica gel and removal of solvent in vacuo gave 0.011 g of a yellow residue, which was chromatographed (7mm x 2" SiO_2, 1-5% ether/methylene chloride gradient) to afford 0.0101 g (80%) of 90 as a yellow oil: IR ($CHCl_3$) 2920, 2850, 1750, 1670, 1620, 1560, 1480, 1370, 1260, 1090, 900 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.04 (s, 6H), 0.84 (s, 9H), 1.17 (d, 3H, J=7), 1.2-2.0 (m, 13H), 2.0-3.1 (m, 4H), 2.43 (s, 3H); MS m/z 608 (M^+), 566, 551, 509; exact mass m/z 608.318 (calcd for $C_{35}H_{48}O_7Si$: 608.317).

(2R,3S,4R,4aS,12aS)-2-Acetyl-3,4-dihydroxy-10,11-dimethoxy-1,2,3,4, 4a,12a-hexahydro-12(5H)-naphthacenone Cyclohexylidene Ketal (93).

Compound 89 (0.0010 g, 0.0017 mmol), potassium carbonate (0.069 g, 0.500 mmol), and dimethyl sulfate (0.026 g, 0.210 mmol) were stirred in acetone (2 mL) for 2 h. The mixture was then refluxed for 8 h. After evaporation of the acetone, ether and triethylamine (0.040 mL) were added and the mixture was allowed to

stand for 1 h. The precipitate was filtered and the solvent was removed to afford a more polar substance, presumed to be 91.

To a solution of presumed 91 (ca. 0.001 g) in tetrahydrofuran (1 mL) was added a 1.00 M solution of tetra-n-butylammonium fluoride in tetrahydrofuran (0.020 mL, 0.020 mmol). After 6 h, the reaction was determined to be complete by TLC analysis. The mixture was added to a saturated aqueous ammonium chloride solution and extracted with ether (3 x). The organic layer was washed with brine and dried (sodium sulfate). Solvent evaporation gave a residue (presumably 92), which was taken up in methylene chloride (1 mL) and stirred with pyridinium chlorochromate (0.015 g, 0.069 mmol). After 3 h, the reaction mixture was diluted with ether, filtered through Celite (7mm x 2"), and concentrated. The residue was chromatographed (7mm x 2" SiO_2, 35% ethyl acetate/hexane) to provide 93 (ca. 0.001 g) as a fluorescent solid: ^1H NMR ($CDCl_3$) δ 2.34 (s), 3.98 (s), 4.05 (s), UV ($CHCl_3$) λ_{max} 264, 341 nm.

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