AN ABSTRACT OF THE THESIS OF

Alexander J. Pallenberg for the degree of Doctor of Philosophy in Chemistry presented on March 16, 1988.

Title: Synthesis of Metabolites from the Ascomycetes:

I. The Synthesis and Absolute Configuration of Leptosphaerin

II. Approaches to the Synthesis of Byssochlamic Acid

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Part I. The total synthesis of (+)-leptosphaerin (**2**), a metabolite of the marine Ascomycete *Leptosphaeria Oraemaris* (Linder) was achieved, unambiguously establishing both the relative and absolute stereochemistry of this natural product. This synthesis also resolved the long-standing question of which of the isomeric structures **1** or **2** correctly represents the structure of leptosphaerin. The target material was prepared in 12 steps, beginning from mannitol and ethyl pyruvate. In the key step a protected form of R-(+)-glyceraldehyde (**3**) underwent a stereospecific condensation with a 3-lithioacrylate derivative (**48**) to give a product (**55**) which was elaborated into leptosphaerin. The stereochemical outcome of this condensation was determined by means of a single crystal X-ray analysis.

Part II. Two synthetic approaches to byssochlamic acid (**3**), a metabolite of *Byssochlamys fulva*, were studied. The first of these was based on a route in which a suitably functionalized 1,5-hexadiene (**23**) was intended to provide the substrate for an intramolecular [2+2] photocycloaddition. The impracticability of obtaining a suitable

photolysis substrate caused revision of this strategy, for which the macrolide **88** became the focal intermediate. The bis phenol **89** was prepared by a sequence of reactions, the key step of which was the samarium diiodide mediated alkylation of 2',5'-dimethoxybutyrophenone (**79**) with 2,5-dimethoxybenzyl bromide (**77**). Reduction of the resulting tertiary alcohol (**80**) was followed by the selective protection of **80** as bisphenol **89**, which underwent esterification with ethylmalonyl dichloride to give macrolide **88**.

Synthesis of Metabolites from the Ascomycetes:

I. The Synthesis and Absolute Configuration of Leptosphaerin

II. Approaches to the Synthesis of Byssochlamic Acid

by

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Synthesis of Metabolites from the Ascomycetes:

I. The Synthesis and Absolute Configuration of Leptosphaerin

II. Approaches to the Synthesis of Byssochlamic Acid

General Introduction

The Ascomycetes are the largest class of fungi with over 15,000 species already known. Members of this class are exploited in brewing and baking, and for the production of antibiotics and vitamins. The morels and truffles, which are considered by some to be delicacies, are Ascomycetes.

In Part I of this dissertation, the synthesis and structure proof of leptosphaerin is presented. This unique metabolite is obtained from *Leptosphaeria Oraemaris* (Linder), a marine Ascomycete found in many parts of the world including Oregon, on the abundant coastal driftwood. The method employed to synthesize this compound used a highly diastereoselective condensation reaction, the outcome of which was shown to be that predicted on the basis of the Felkin-Ahn model. In this way the relative and absolute stereochemistry of leptosphaerin was unambiguously demonstrated.

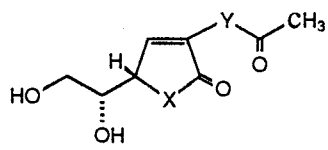
Part II contains a description of our efforts toward the synthesis of byssochlamic acid. This metabolite is a member of a class of natural products called nonadrides. Byssochlamic acid itself is obtained from the Ascomycete *Byssochlamys fulva* . This organism, as well as those producing several other nonadrides, are found in soil, in canned fruit and vegetables, and in animal feed which has not been stored or preserved properly. The discussion in Part II first details a strategy based on the photolysis of a 1,5-hexadiene derivative. This approach was eventually abandoned due to the difficulties encountered in generating a suitable substrate. Subsequently, we undertook a study based on the generation of a 13-membered bis lactone which we foresee as a potential precursor of byssochlamic acid by a double Fries rearrangement.

Part I: The Structure and Absolute Configuration of Leptosphaerin

I-A. Introduction

Although the search for natural products has traditionally been motivated by the need for biologically active materials[1] the characterization of such products can also contribute greatly to the understanding of the taxonomic relationships between naturally occurring compounds.[2] Despite the vastness of our oceans, investigation of the varied chemical resources present therein has, until recently, lagged behind the study of terrestrial natural products.[3]

The metabolic capabilities of terrestrial fungi have been extensively studied[4] while those of the marine fungi have been examined to a much lesser extent.[5] It was for this reason that previous workers in our group[6] undertook a determination of the structure of leptosphaerin, a metabolite of the marine Ascomycete *Leptosphaeria oraemaris* (Linder). Thus, a liquid culture of *L. oraemaris* was concentrated and extracted with ethyl acetate. Chromatographic purification of the extracted material gave a white crystalline solid with a melting point of 189.5-190.5°C. The NMR spectrum of this substance revealed the presence of the $HOCH_2CH(OH)$- spin system as well as an acetyl group. This spectrum, in combination with UV data (λ_{max} 246 nm), also revealed that leptosphaerin possesses an α,β-unsaturated carbonyl system bearing a substituent in the α position. The infrared spectrum of leptosphaerin showed

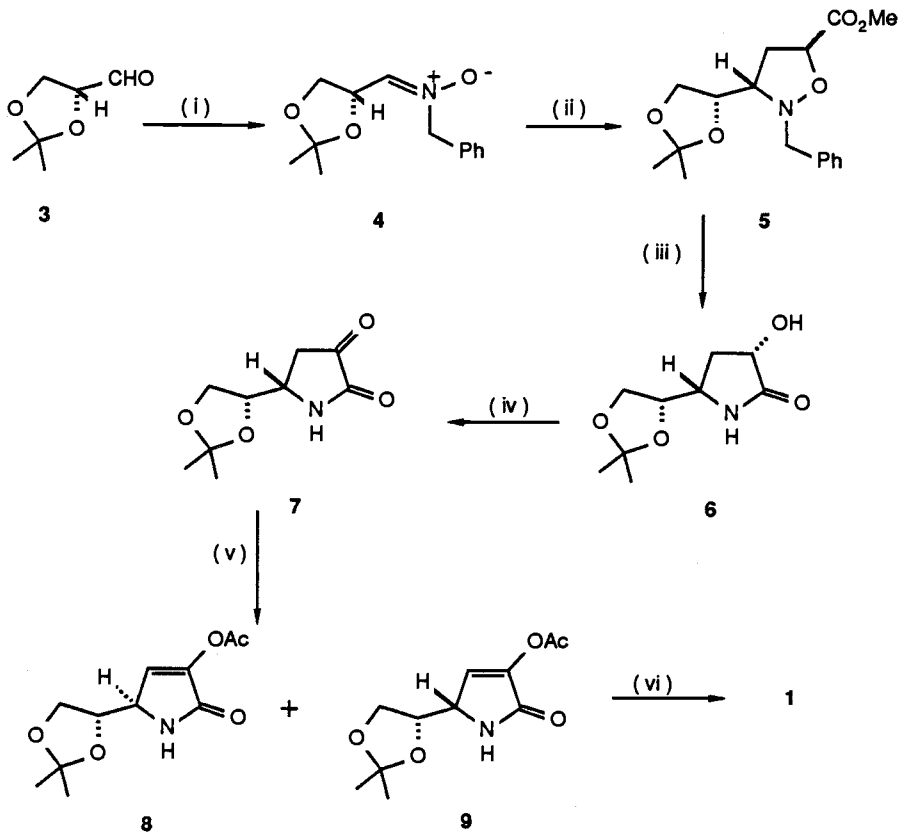


1 X = NH, Y = O
2 X = O, Y = NH

the presence of -OH and -NH protons. The carbonyl region of the infrared spectrum

(1745, 1670, 1640 cm^{-1}), coupled with the above information suggested either **1** or **2** as the structure of leptosphaerin.

In the hope of resolving this structural ambiguity a synthetic approach to **1** was undertaken as shown in Scheme 1. (R)-Glyceraldehyde acetonide[7] reacted with N-



(i) $PhCH_2NHOH$, $CHCl_3$, 79%; (ii) CH_2=$CHCO_2Me$, reflux, 97%; (iii) H_2, Pd/C, 51%; (iv) DMSO, DCC, H_3PO_4; (v) Ac_2O, pyr., 58% from **6** ; (vi) $(CO_2H)_2$, H_2O.

Scheme 1

benzylhydroxylamine[8] to afford nitrone **4**.[9] Cycloaddition of this material with methyl acrylate gave isoxazolidine **5** which was reduced to the hydroxy lactam **6**. Moffatt oxidation, followed by acetylation, gave a 1:3 mixture of **8** and **9**. Treatment of **9** with aqueous acid gave **1**, the spectral properties of which were quite different from leptosphaerin. On this basis it was concluded that the structure of leptosphaerin is, in

fact, **2**. The structure **2** appears consistent with the observation[10] that amino sugars are almost always found as the N-acetyl derivatives. This conclusion was reinforced by an x-ray crystallographic analysis[11] of the natural material.

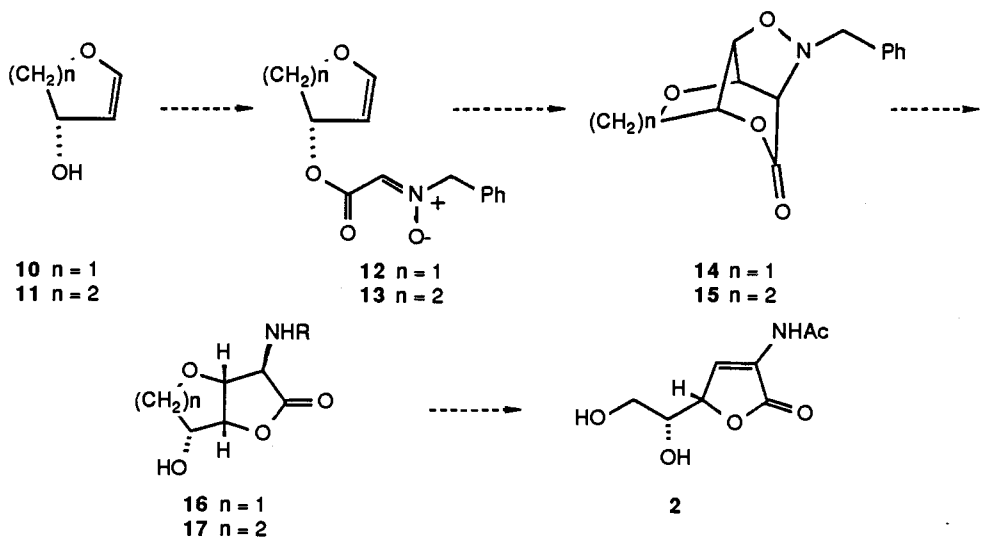
Lactone **2** has been postulated as one of the compounds obtained upon basic hydrolysis of the oxidation products of N-acetylmannosamine with bromine.[12] While the data reported agree to some extent with those of leptosphaerin, we were unable to isolate this material from the large number of products obtained in this sequence. It was therefore concluded that this route did not conclusively establish the structure of leptosphaerin. The purpose of the present investigation, then, was to synthesize **2** unambiguously and thereby provide final and definitive proof of the structure of leptosphaerin.

I-B. Discussion

Inspection of structure **2** reveals that it possesses two contiguous chiral centers, each having one oxygen substituent. We therefore retained the notion throughout this investigation that these two centers, at a minimum, should be derived from a carbohydrate precursor. The array of functionality in the lactone ring, however, could be viewed in several ways.

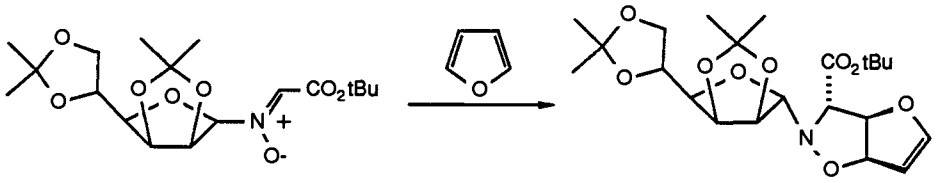
At the outset our synthetic strategy was guided by the recognition that leptosphaerin is a dehydro amino lactone, possibly derived from an enamine of an α-ketoester, the simplest source of which is the pyruvate system (vide infra). A number of methods are also known for producing enamides of this type directly from the corresponding α-amino acid.[13] However, it was decided to begin with an approach based on cycloaddition chemistry, as we had with the synthesis of **1**, because such processes frequently allow excellent stereocontrol.

This approach was built around the use of a nitrone cycloaddition, as shown in



the conversion of **12/13** to **14/15** . For this plan we sought a suitable glycal which could be converted to its glyoxylate ester and then to the corresponding nitrone **12** or **13** by reaction with N-benzylhydroxylamine. Thermal cycloaddition of such a nitrone

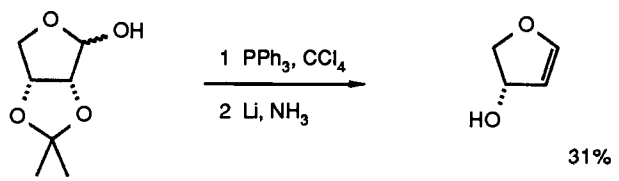
would give bridged isoxazolidine **14** or **15**, which would undergo reduction and rearrangement to give lactone **16** or **17**. Intermolecular nitrone cycloadditions have



18 **19**

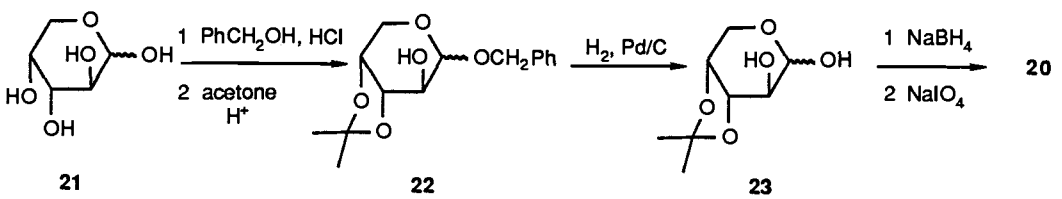
been found by Vasella[14] to give the regiochemistry postulated in the reaction of **12** and **13** as shown by his conversion of **18** to **19**. Accordingly, synthetic strategies that would generate both the 5- and 6-membered glycals **10** and **11** were investigated.

The appropriate furanoid glycal **10** was prepared by the method of Ireland[15] from erythrose acetonide **20.** This gave the allylic alcohol **10** in 31% yield for the two



20 **10**

steps. Compound **20** was prepared in 50% overall yield from D-arabinose by the well

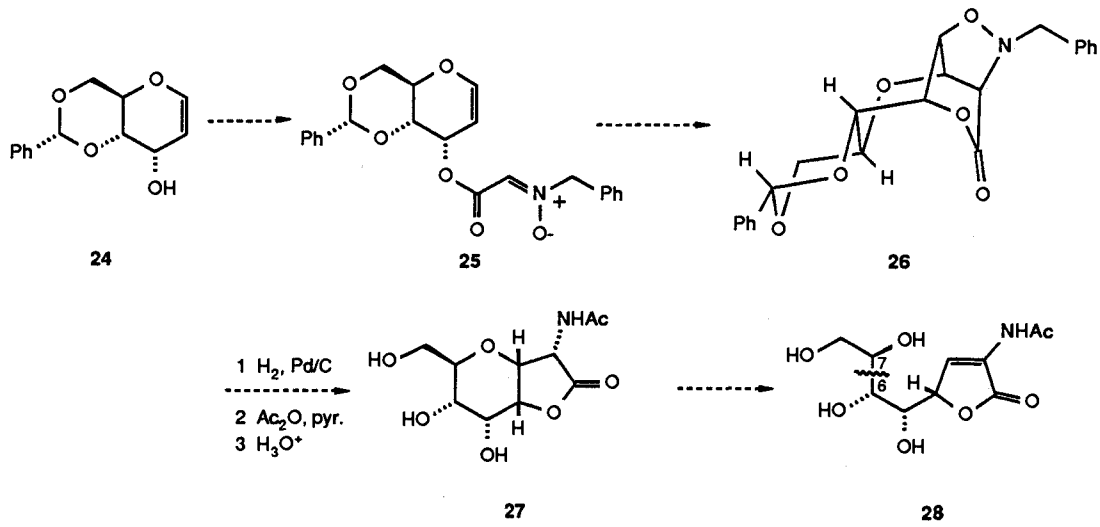


21 **22** **23**

known method of Ballou.[16] Unfortunately, all attempts to prepare esters of **10** led to the formation of tarry materials and this series was therefore abandoned.

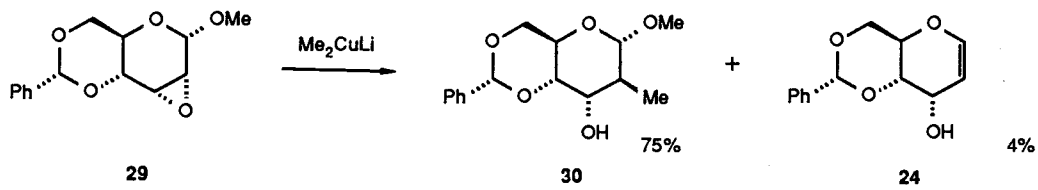
In the case of the pyran route from **11** an analogous nitrone **25** could be employed to generate, by thermolysis, catalytic hydrogenation, acetylation, and acid treatment, the lactone **27**. Elimination to **28** and a subsequent oxidative cleavage at C-6/7 could then be employed to give **2.**

Of some concern was the fact that although pyranoid glycals are known,[17] few are conveniently available with any differentiation between the three hydroxyl groups.[18] Allylic alcohol **24** is available from tri-O-acetyl-D-glucal by saponification of all three acetate groups, followed by selective benzylidene acetal formation, in 21% overall yield.[17a] We felt that the yield and cost of starting material for this conversion



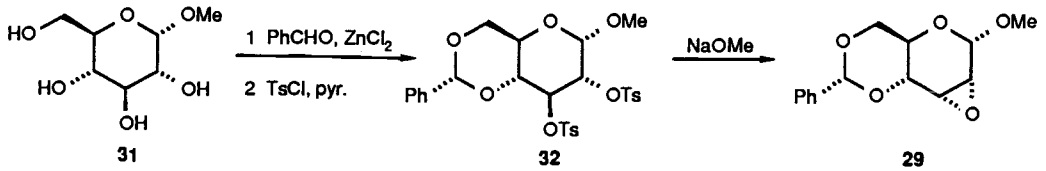
were less than ideal but, more importantly, the use of a low yielding sequence of protecting group manipulations was aesthetically unacceptable. Accordingly, we sought an alternative protocol for entry to this system.

We found that the desired allylic alcohol **24** was obtained as a minor side



product in the addition of lithium dimethyl cuprate to epoxide **29**.[19] Clearly this product arose via an electron transfer process which competes with the usual nucleophilic epoxide opening. It seemed reasonable in this light that treatment of **29** with a more efficient electron transfer reagent might be a good means by which to carry out this transformation. One reagent which came readily to mind was samarium

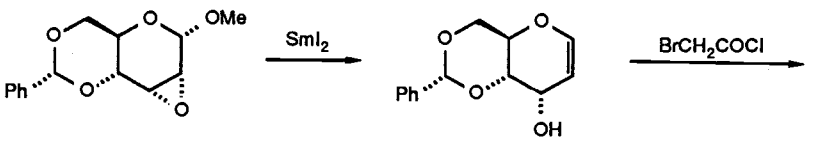
diiodide, a reducing agent with a prodigious reduction potential (-1.17v), excellent solubility properties, and which is easily prepared.[20] Epoxide **29** is readily available



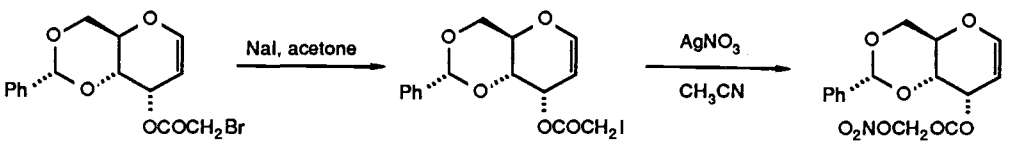
31 **32** **29**

via a known[21] sequence of three transformations from α-methyl-D-glucoside (**31**) via **32** in 43% overall yield.

Reduction of **29** with samarium diiodide in tetrahydrofuran proceeded smoothly to afford an 86% yield of the allylic alcohol **24**. Application of the procedure of



29 **24**

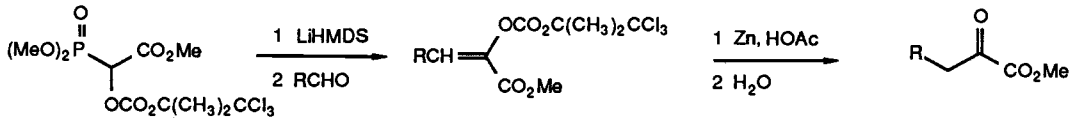


33 **34** **35**

Kornblum[22] for generating glyoxylate esters required first the formation of a nitrate such as **35**. Thus the bromoacetate ester **33** of alcohol **24** was prepared but, due to its very low reactivity toward silver nitrate, it was necessary to convert this compound to iodoacetate **34**. This reacted smoothly to give the nitrate **35** in good yield. However, efforts to obtain a glyoxylate from this material gave, in every instance, intractable polar products.

The unexpected difficulties encountered in routes departing from glycals **10** and **11** rendered an approach to leptosphaerin based on nitrone cycloadditions impracticable. For this reason, we began to investigate a strategy based on a different retrosynthetic analysis. This was centered on the disconnection of the C_2-C_3 bond of

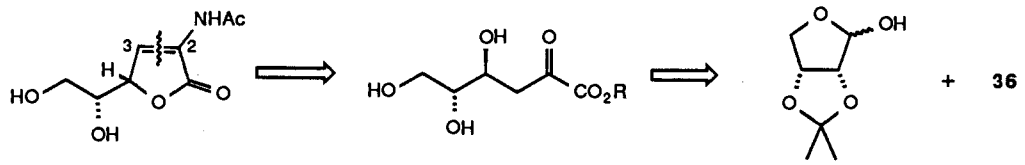
leptosphaerin. Thompson, in his approach to the tremorgenic mycotoxins,[23] developed



36 37 38

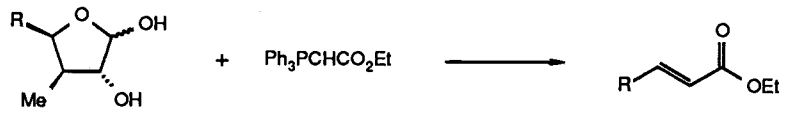
Scheme 2

a rather general method for the preparation of α-ketoesters (such as **38**) via a Horner-



2 39 20

Emmons phosphonate olefination as shown in Scheme 2. While we could find no examples of this particular reaction using a hemiacetal in place of an aldehyde, we thought that this transformation would occur by analogy to the well known work of

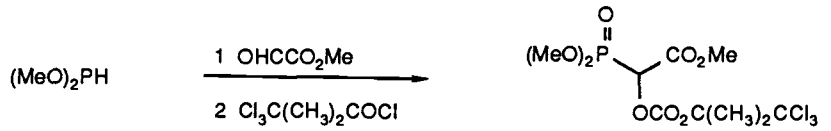


40 41 42

Nicolaou,[24] in which the hemiacetal **40** was converted to **42** in 82% yield with the ylid **41**.

Accordingly the phosphonate **36** was prepared using Thompson's procedure. Deprotonation of **36** with lithium hexamethyldisilazide, followed by treatment with erythrose acetonide (**20**), gave **43** and **44** in 4% and 15% yield respectively. These compounds were tentatively identified on the basis of their ^{1}H and ^{13}C NMR spectra. The 400MHz NMR spectrum of lactone **44** clearly shows couplings of the H4-H5-H6-H6 spin system while, in the acyclic derivative **43,** these couplings are very poorly defined. In addition, the ^{1}H spectrum of the more polar (by silica gel chromatography) product **43** has a methyl singlet at δ 3.8 which is absent in the spectrum of **44**.

It was our hope that after removal of the acetonide from **43** and **44** the more favorable γ - lactone **45** could be formed preferentially, or that under conditions of



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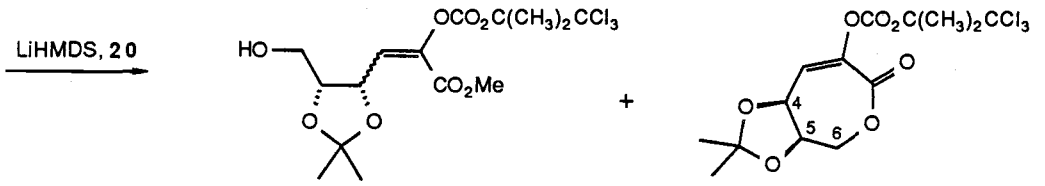
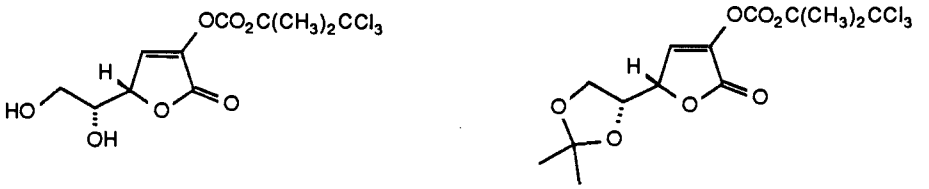


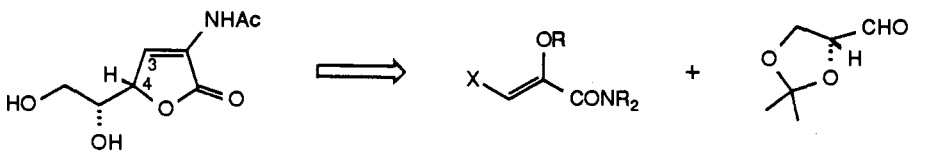
43 **44**



45 **46**

acetonide formation the terminal ketal γ-lactone form **46** could be obtained. However, attempts to obtain these results met uniformly with failure.

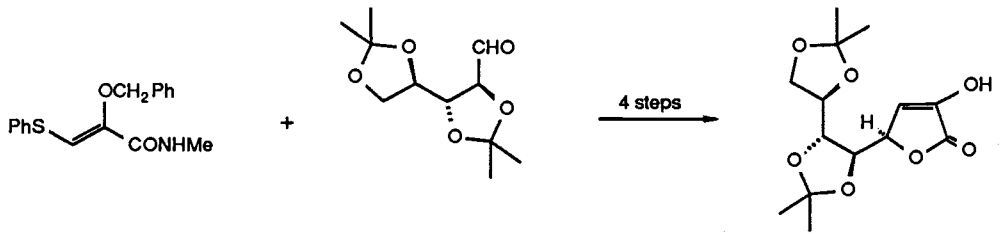
The final, and ultimately successful, approach to leptosphaerin is based on



2 **47** **3**

disconnection of the C_3-C_4 bond of the lactone ring of leptosphaerin.[25] Deprotonation of a suitable acrylate derivative **47** at position 3 and condensation with **3** would allow all the necessary chiral centers of the target to be derived from a carbohydrate

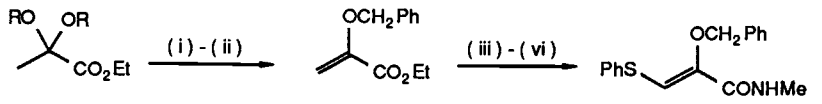
precursor, yet does not require an inordinate amount of functional group manipulation of the source carbohydrate. It has been shown by Schmidt[26] that the dilithio dianion of



48 49 50

48 condenses in a highly diastereoselective manner with carbohydrate derived aldehydes (such as **49**) having a chiral center α to the carbonyl group. Schmidt also described the manipulations necessary to obtain **48** and to remove the phenylthio and benzyloxy groups once condensation has taken place.

The diethyl ketal **51**[27] of ethyl pyruvate, was converted to the acrylamide derivative **48** by the method of Betz.[28] Thus, transketalization to the dibenzyl ketal **52**

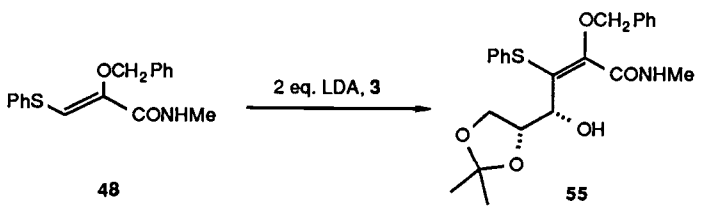


51 R = Et
52 R = CH_2Ph

53 **48**

(i) $PhCH_2OH$, $KHSO_4$, 77%; (ii) P_2O_5, DMF, 8 2%; (iii) PhSH, $(nBu)_4NF$, 44%; (iv) NCS, CCl_4; (v) Et_3N, $CHCl_3$; (vi) $MeNH_2$, MeOH, 65%(3 steps).

followed by elimination gave ethyl 2-benzyloxyacrylate **53**. Thiophenol undergoes fluoride catalyzed Michael reaction with **53** which, followed by Pummerer oxidation and amide formation then furnished **48** in 18% overall yield from ethyl pyruvate.

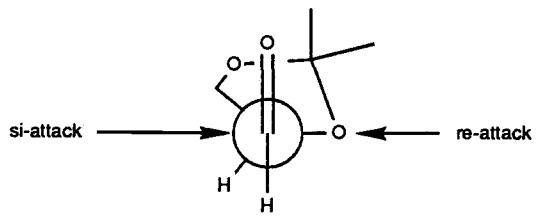


48 **55**

Deprotonation of **48** at -78°C to its dianion and subsequent treatment with the

acetonide **3** of R-(+)-glyceraldehyde at low temperature gave a single crystalline product **55** in high yield.

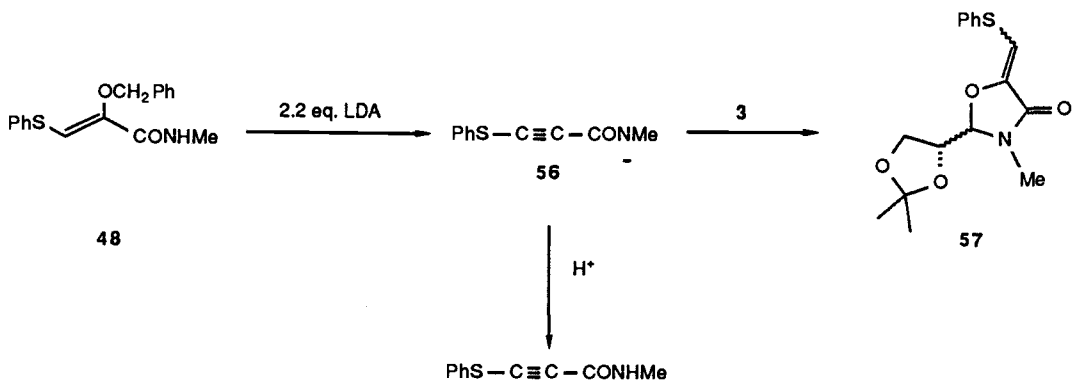
Analysis of the reaction of **3** with **48** according to the Felkin-Ahn model[29] leads to the prediction that **55** should possess 4R (erythro) stereochemistry arising via



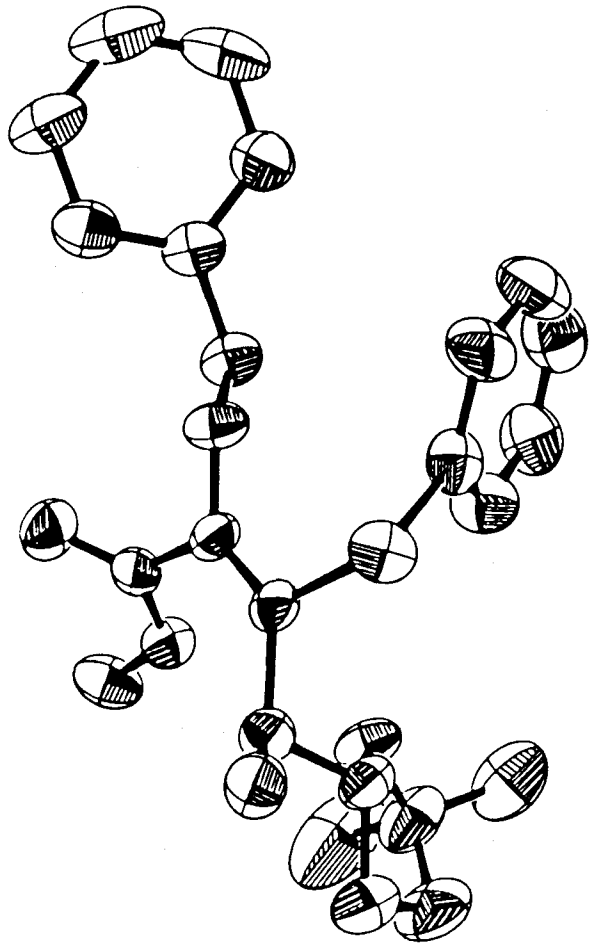
3

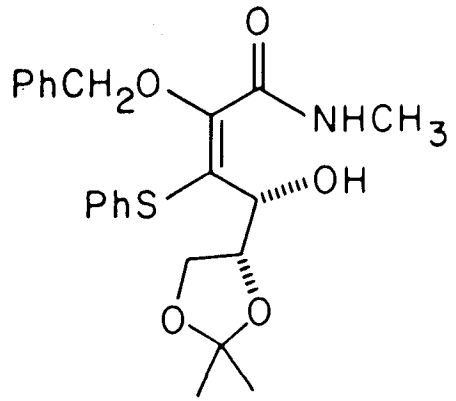
attack of the nucleophile at the *si* face of the carbonyl group of **3** - leading to formation of **55**. That this was indeed the case was verified by a single crystal X-ray analysis of **55**.[30]

Interestingly, a very different pathway is seen when **48** and **3** react at higher temperature. During initial attempts to effect the condensation of acrylamide **48** with **3**, the former was treated with 2.2 equivalents of lithiumdiisopropyl amide and warmed to 0°C for a short time. If the reaction mixture was then cooled back to -78°C and the



aldehyde **3** was added, a 56% yield of a material found to be oxazolidinone **57** was obtained. The structural assignment of **57** is based upon NMR, IR, and combustion analysis data. The 400MHz ^{1}H NMR spectrum of **57** clearly shows the absence of the





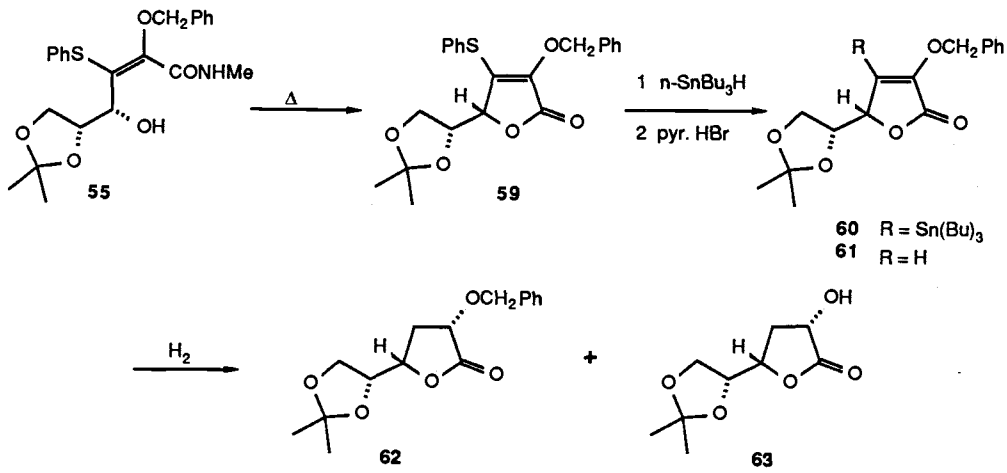
55

Figure I-1. ORTEP view of **55**

benzyloxy substituent, while the glyceraldehyde acetonide moiety remains intact except for the aldehyde proton itself (shifted upfield to δ 5.09). The infrared spectrum of **57** shows carbonyl frequencies (1667 and 1583cm^{-1}) consistent with the presence of an α,β-unsaturated amide as well as the absence of OH or NH groups. Elemental analysis for $C_{16}H_{19}NO_4S$ is consistent with structure of **57**.

The oxazolidinone **57** was first thought to arise from reaction of the monoanion of **48** with **3**. However, when the reaction was quenched before addition of the aldehyde there was obtained the propiolamide **58** (IR 2140, 1660, ^{1}H NMR for phenyl, methyl, and broad NH only) in 88% yield. Clearly **58** is formed from dianion of **48** by net loss of lithium benzyloxide. Subsequent reaction of **56** with **3** then gives **57**.

With the amide **55** in hand the construction of the butenolide ring could be undertaken. Heating a solution of **55** in n-octane[31] at reflux resulted in irreversible lactonization via loss of methylamine to give **59** in 87% yield. For the purpose of removing the phenylthio group, **59** was first converted to its tri-n-butylstannyl analogue **60** with tri-n-butyltin hydride. Attempted protodestannylation of this

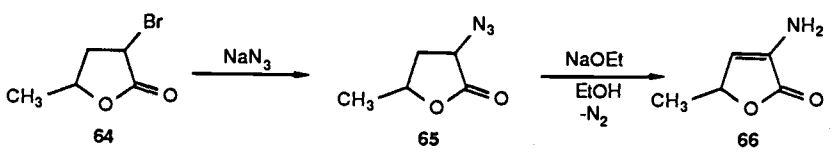


intermediate with anhydrous hydrogen bromide[32] led only to destruction of the

material. However, the conversion of **60** to **61** could be effected in good yield by heating with pyridine hydrobromide.

It was our intention at this juncture to debenzylate enol ether **61** by hydrogenolysis and convert the resulting α-keto lactone to the corresponding enamide. In practice, hydrogenation of the double bond of **61**, to give benzyl ether **62**, was observed to be a far more rapid reaction than hydrogenolysis of the benzyl group under a wide variety of conditions, and in conflict with the reported results of Schmidt.[26] This unexpected discovery forced a reconsideration of the tactics envisioned for the final stages of the synthesis. The unavailability of an α-keto lactone from **61** suggested that a new route to **70** through the alcohol oxidation level would be necessary.

Hydrogenation of **61** under more forcing conditions (such as a long reaction time or use of palladium hydroxide as catalyst) afforded alcohol **63** quantitatively. With this alcohol secure we turned our attention to its conversion to enamide **70**. Model

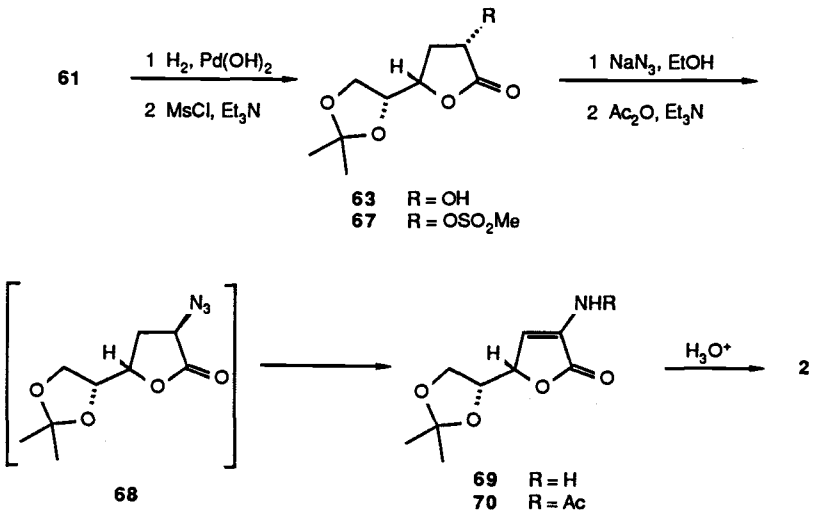


64 65 66

studies performed by Dr. Badger in our group[33] and based upon the work of Kraatz, et al[34] suggested that the desired transformation could be effected via an α-azidolactone corresponding to **65**. In this model study α–bromo-γ-valerolactone **64** was converted to azidolactone **65** upon treatment with ethanolic sodium azide. This, in turn, was treated with sodium ethoxide to give enamine **66** by loss of nitrogen.

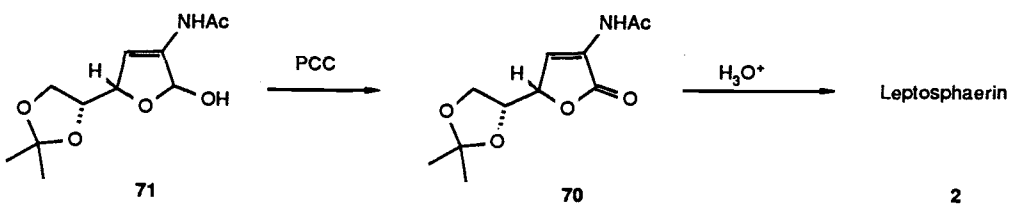
In analogy with this model sequence, alcohol **63** was activated by conversion to its mesylate **67**, which was treated with sodium azide. The intermediate azidolactone **68** could not be isolated but underwent spontaneous loss of nitrogen to give the unstable enamine **69.** This was isolated in stable form as enamide **70** after treatment with acetic anhydride. Hydrolysis of **70** under mild conditions afforded synthetic

leptosphaerin **2**, which was identical to naturally derived material in its infrared and



NMR spectra, melting point, optical rotation, and chromatographic behavior.

It is interesting to compare these results with a recently reported[35] preparation of leptosphaerin by Rollin, in which acetonide **70** was formed in the penultimate step by oxidation of lactol **71** with pyridinium chlorochromate. Rollin claims mp 79-80°C



and α_D -10.5° for **70**, which is clearly inconsistent with our data (mp 128-129°C and α_D −51°). This discrepancy suggests that Rollin's material is inhomogeneous. Based on the results on Pravdic and Fletcher[12] it seems probable that epimerization occurred in the oxidation used by Rollin to obtain **70** and led to a mixture of **70** and its C-4 epimer. Whether the resulting mixture was separable at this stage or at the stage of the final product is not disclosed by Rollin, but it is unclear how an intermediate of such low purity could cleanly yield leptosphaerin with properties similar to those published for the pure natural product.

That leptosphaerin is indeed 2-acetamido-2,3-dideoxy-D-erythro-hex-2-enoic acid γ-lactone (2) as proposed is established by the synthesis of this substance. The assignment of 4S, 5R absolute configuration to leptosphaerin is consistent with its biogenesis from a sugar of the D-series via transamination and dehydration. Both chiral centers of leptosphaerin have the same configuration as the corresponding centers in D-glucose.

I-C. Experimental Section

All solvents for routine chromatography and reaction workup were reagent grade and were distilled through glass. Solvents for reactions were dried by distillation from an appropriate drying agent shortly before use. Tetrahydrofuran, ether, benzene, and toluene were distilled from potassium benzophenone ketyl under argon. Methylene chloride, triethylamine, diisopropylamine, pyridine, dimethyl sulfoxide, and dimethyl formamide were distilled from calcium hydride under argon. Starting materials and reagents were obtained from commercial suppliers unless otherwise noted.

Reaction flasks were oven-dried overnight at or above 165°C or flame dried and cooled in a desiccator over anhydrous calcium sulfate immediately prior to use. Syringes were oven-dried overnight and cooled in a desiccator as above. Removal of solvent was carried out under water aspirator pressure with a rotary evaporator and residual solvent was removed at the vacuum pump.

Flash chromatography was performed using E. Merck silica gel 60 (230-400 mesh ASTM) and an elution rate of approximately 2 inches per minute as described by Still.[36] Analytical thin layer chromatography was carried out with E. Merck precoated TLC plates (silica gel 60 F-254, 0.2mm layer thickness) cut to a size of 2.5 x 6.7 cm.

Nuclear magnetic resonance (NMR) spectra were obtained using either an IBM NR-80F or a Bruker AM-400 spectrometer. Chemical shifts are reported downfield from tetramethylsilane used as internal standard on the δ scale. ^{1}H NMR data are given in the following order: integral, multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; p, pentet; m, multiplet; b, broad), and coupling constant in Hertz. Infrared spectra (IR) were recorded on a Nicolet 5DXB FT instrument or a Perkin-Elmer 727B grating instrument. Optical rotations were determined with a Perkin-Elmer 243 polarimeter using cells of 1 decimeter pathlength and 1 mL capacity. Routine mass spectra (MS) were measured on either a Varian MAT CH-7 or a Finnigan 4500

spectrometer using electron impact ionization at a potential of 70 eV. Exact mass measurements were performed with a Kratos MS-50 spectrometer. Melting points were determined with a Büchi melting point apparatus and are uncorrected. Elemental analyses were performed by Desert Analytics of Tucson, Arizona.

1,5-Anhydro-2-deoxy-4,6-O-(phenylmethylene)-D-ribohex-1-enitol (24)

To a stirred suspension of powdered samarium metal (5.4g, 36 mmol) in dry, oxygen-free tetrahydrofuran (30mL) was added a solution of 1,2-diiodoethane (5.07g,18mmol) in tetrahydrofuran (450mL) dropwise until a blue color formed. At this time the remaining diiodoethane solution (ca. 400mL) was added rapidly. The resulting mixture was stirred overnight at room temperature. The dark blue samarium diiodide solution was then added via cannula to an ice-cooled solution of **29** (1.70g, 6.5mmol) in tetrahydrofuran (50mL). After stirring 45min. at 0°C the mixture was stirred at room temperature for 8h. The resultant dark blue solution was poured into 1M ammonium acetate (500mL) and this mixture was extracted with chloroform (4 x 200mL). The combined chloroform extracts were dried over magnesium sulfate, filtered, and evaporated to give 2.0g of an amber oil. Flash chromatography on silica (25→50% ethyl acetate-hexanes) gave 1.17g (78%) of **24** as a white crystalline solid: mp 83-84°C(lit.[16b] 84-85°C); $[\alpha]_D$ +195.6°(c 2.14, $CHCl_3$); IR (film) 3500, 3060, 3040, 2980, 2860, 1640cm^{-1}; ^1H NMR (400MHz, $CDCl_3$) δ 7.51 (2H, m), 7.39 (3H, m), 6.45 (1H, d, J=6.01), 5.67 (1H, s), 5.02 (1H, dd, J=5.85, 6.01), 4.47 (1H, dd, J=5.24, 10.48), 4.22 (2H, m), 3.84 (2H, m); ^{13}C NMR (20MHz, $CDCl_3$) δ 146.4, 137.5, 129.4, 128.5, 126.4, 102.0, 101.3, 78.3, 68.7, 64.0, 60.2; MS *m/z* 234(M+), 105, 71; Calcd for $C_{13}H_{14}O_4$: 234.0892. Found: 234.0906.

4,6-O-Benzylidene-3-bromoacetyl-D-allal (33)

To a solution of allylic alcohol **24** (460mg, 1.96mmol) in methylene chloride (20mL) and pyridine (1mL) at 0°C was added bromoacetyl chloride (0.62g, 320μL, 3.90mmol) and 4-(dimethylamino)pyridine (cat.) with stirring. After 0.5h at this temperature the reaction mixture was subjected directly to flash chromatography on silica (25% ethyl acetate-hexanes) to afford 624mg (89%) of bromoacetate **33** as a white crystalline solid: mp 103.5-104°C; $[\alpha]_D$ +241.8°(c 2.4, $CHCl_3$); IR (film) 2860, 1760, 1640cm^{-1}; ^1H NMR (400MHz, $CDCl_3$) δ 7.45 (2H, m), 7.37 (3H, m), 6.53 (1H, d, J=6.02), 5.61 (1H, s), 5.48 (1H, m), 5.03 (1H, dd, J=5.95, 6.05), 4.46 (1H, dd, J=5.21, 10.55), 4.18 (1H, m), 4.09 (1H, s), 4.01 (1H, dd, J=10.5, 3.8), 3.87 (1H, s), 3.85 (1H, dd, J=9.6, 10.8); ^{13}C NMR (20MHz, $CDCl_3$) δ 167.4, 148.7, 137.7, 129.6, 128.7, 126.6, 102.1, 98.1, 76.2, 68.9, 65.4, 64.3, 41.0; MS *m/z* 217, 105, 91.

4,6-O-Benzylidene-3-iodoacetyl-D-allal (34)

To a solution of **33** (64mg, 0.18mmol) in dry acetone (1mL) was added sodium iodide (81mg, 0.54 mmol) and the mixture was stirred at room temperature for 24h. The mixture was filtered through silica (elution with ether), dried over magnesium sulfate, and evaporated to give 73mg (100%) of **34** as a white crystalline solid: mp 73.5-74°C(ether/hexanes); $[\alpha]_D$ +224.6°(c 4.7, $CHCl_3$); IR (film) 3050, 2980, 2870, 1735, 1638cm^{-1}; ^1H NMR (400MHz, $CDCl_3$) δ 7.48 (2H, m), 7.34 (3H, m), 6.52 (1H, d, J=5.90), 5.59 (1H, s), 5.42 (1H, dd, J=5.86, 3.88), 5.00 (1H, dd, J=5.90, 5.86), 4.46 (1H, dd, J=5.24, 10.58), 4.21 (1H, ddd, J=10.4, 10.5, 5.25), 4.00 (1H, dd, J=3.85, 10.55), 3.83 (1H, dd, J=10.5, 10.4), 3.71 (2H, s); ^{13}C NMR (20MHz, $CDCl_3$) δ 168.3, 148.2, 137.2, 129.2, 128.3, 126.4, 101.8, 97.6, 76.0, 68.5, 64.9, 63.8, -5.7; MS *m/z* 402(M+), 185, 169, 127, 105, 91, 62. Calcd for $C_{15}H_{15}IO_5$: 401.9964. Found: 401.9964.

Nitratoacetyl-4,6-O-benzylidene-D-allal (35)

A solution of iodoacetate **34** (74mg, 0.18mmol) and silver nitrate (300mg, 1.77mmol) in acetonitrile (0.5mL) was stirred at room temperature for 4h. This mixture was diluted with water (25mL) and extracted with ether (4 x 25mL). The combined ethereal extracts were dried over sodium sulfate, filtered, and evaporated to give 60mg of a colorless oil. Flash chromatography on silica (25% ethyl acetate-hexanes) gave 57mg (92%) of **35** as a white crystalline solid: mp 71.5-72°C; $[\alpha]_D$ +213°(c 2.1, $CHCl_3$); IR (film) 2940, 2870, 1760, 1660, 1645, 850, 755, 700cm^{-1}; ^1H NMR (400MHz, $CDCl_3$) δ 7.43 (2H, m), 7.37 (3H, m), 6.54 (1H, d, J=6.01), 5.61 (1H, s), 5.54 (1H, dd, J=5.90, 3.82), 5.01 (1H, dd, J=5.90, 6.01), 4.91 (2H, s), 4.47 (1H, dd, J=5.15, 10.55), 4.14 (1H, ddd, J=5.15, 10.35, 10.71), 4.02 (1H, dd, J=3.82, 10.71), 3.85 (1H, dd, J=10.55, 10.35); ^{13}C NMR (100MHz, $CDCl_3$) δ 165.5, 148.4, 136.7, 129.3, 128.3, 126.0, 101.7, 97.3, 75.6, 67.0, 65.0, 64.0; MS *m/z* 337(M+), 105, 91; Calcd for $C_{15}H_{15}NO_8$: 337.0798. Found: 337.0782. Anal. Calcd for $C_{15}H_{15}NO_8$: C, 53.42; H, 4.48; N, 4.15. Found: C, 53.27; H, 4.45; N, 3.93.

Enol Carbonates (43) and (44)

To a solution of hexamethyldisilazane (0.242g, 0.316mL, 1.50mmol) in tetrahydrofuran (5mL) was added a 1.55M solution of n-butyllithium in hexanes (0.96mL, 1.50mmol) and the mixture was stirred 15min. at room temperature. The resulting solution of lithium hexamethyldisilazide was cooled to -78°C and to it was added a solution of the protected phosphonate **36** (0.50g, 1.25mmol) in tetrahydrofuran (5mL) dropwise. After the addition was complete the solution was stirred for a further 10min. at -78°C before **20** (0.20g, 1.25mmol) was rapidly added. The reaction mixture was stirred 1h at 0°C and diluted with ether (50mL). This solution was washed with 3N hydrochloric acid (10mL) and saturated aqueous sodium

bicarbonate (15mL). The resulting ethereal solution was dried over magnesium sulfate, filtered, and evaporated to give 506mg of an amber oil. Flash chromatography of this oil on silica (10→50% ethyl acetate-hexanes) gave 75mg (15%) of **44** as a white solid followed by 41mg (4%) of **43** as a colorless oil; **43**: ^{1}H NMR (400MHz, $CDCl_3$) δ 6.2 (1H, d, J=8), 4.9-3.9 (4H, m), 3.8 (3H, s), 2.0 (6H, s), 1.5 (3H, s), 1.4 (3H, s); **44:** ^{1}H NMR (400MHz, $CDCl_3$) δ 6.06 (1H,s), 4.88 (1H, dd, J=5.8, 3.5), 4.78 (1H, d, J=5.8), 4.15 (1H, d, J=10.7), 4.07 (1H, dd, J=3.5, 10.7), 1.95 (3H, s), 1.94 (3H, s), 1.49 (3H, s), 1.33 (3H, s); ^{13}C NMR (100MHz, $CDCl_3$) δ 150.8, 113.0, 105.3, 104.6, 90.4, 84.5, 79.4, 73.9, 26.2, 24.8, 21.1, 21.0.

Ethyl Pyruvate Diethyl Ketal (51)

To a solution of ethyl pyruvate (116.6g, 110mL, 1.00 mol) and triethyl orthoformate (155g, 175mL, 1.05mol) in absolute ethanol (150mL) was added p-toluenesulfonic acid (2.4g, cat.) Ethyl formate was distilled (56-62°C) from this mixture until the theoretical amount (75mL) had been obtained (2.5h). The resulting solution was neutralized with triethylamine (2mL) and the ethanol was removed under reduced pressure. The residue was distilled to give 109.9g (58%) of **51** as a colorless liquid: bp 80°C @ 10mm/Hg (lit.[26] 85°C @ 12mm/Hg); IR (film) 2980, 2940, 1755, 1375, 1140cm^{-1}; ^{1}H NMR (400MHz, $CDCl_3$) δ 4.26 (2H, q, J=7.1), 3.3-3.5 (4H, m), 1.54 (3H, s), 1.32 (3H, t, J=7.0), 1.24 (6H, t, J=7.1); ^{13}C NMR (20MHz, $CDCl_3$) δ 170.5, 100.3, 61.3, 58.3, 22.2, 15.4, 14.3.

Ethyl Pyruvate Dibenzyl Ketal (52)

A mixture of **51** (100g, 102mL, 0.526mol), benzyl alcohol (280g, 268mL, 2.59mol), and potassium hydrogen sulfate (1.75g) was heated at a bath temperature of 100°C. Ethanol was distilled from the reaction mixture in a slow stream of argon for 6h, when 27mL had been collected. The resultant mixture was diluted with ether (250mL) and filtered through a plug of silica with ether elution. The ether was removed

under water aspirator pressure. Benzyl alcohol was distilled from the mixture at 70°C and 4.8mm/Hg. Finally, the product distilled at 176°C and 0.09mm/Hg (lit.[27] 135-140°C @ 0.01mm/Hg) to give 128g (77%) of **52** as a colorless oil: IR (film) 3070, 3030, 2980, 2940, 1755, 1500, 1455, 1375, 1140, 1040cm^{-1}; ^{1}H NMR (400MHz, $CDCl_3$) δ 7.35 (10H, m), 4.65, 4.60 (4H, AB, J=11.7), 4.25 (2H, q, J=7.0), 1.67 (3H, s), 1.31(3H,t, J=7.0); ^{13}C NMR (20MHz, $CDCl_3$) δ 169.4, 138.0, 128.2, 127.5, 127.3, 100.1, 64.5, 60.9, 21.7, 13.5.

Ethyl 2-Benzyloxyacrylate (53)

To a solution of **52** (60.0g, 191mmol) in dimethylformamide (150mL) was added phosphorus pentoxide (14.6g, 103mmol) with vigorous mechanical stirring. The mixture was stirred at 100°C for 1h, cooled, and poured into saturated aqueous sodium carbonate (300mL). After gas evolution had ceased the solution was extracted with ether (4 x 50mL). The combined extracts were washed with water (50mL), dried over magnesium sulfate, and evaporated to give 46.3g of an amber oil. Vacuum distillation of this material afforded 32.4g (82%) of **53** as a colorless oil: bp104°C @ 0.09mm/Hg (lit.[27] 85-87°C @ 0.01mm/Hg); IR (film) 3060, 2970, 2930, 1730, 1620, 1180, 1020cm^{-1}; ^{1}H NMR (400MHz, $CDCl_3$) δ 7.38-7.28 (5H, m), 5.39 (1H, d, J=2.6), 4.85 (2H, s), 4.65 (1H, d, J=2.6), 4.25 (2H, q, J=7.3), 1.30 (3H, t, J=7.3); ^{13}C NMR (20MHz, $CDCl_3$) δ 162.8, 151.0, 136.0, 128.2, 128.1, 127.7, 127.4, 127.0, 94.0, 70.0, 60.7, 13.4.

Ethyl 2-Benzyloxy-3-phenylthiopropionate (54)

A solution of **53** (30.0g, 145.5mmol), thiophenol (17.0mL, 163mmol), and tetrabutylammonium fluoride (1M in tetrahydrofuran, 2mL) was heated at reflux for 24h. At this time a further portion of the tetrabutylammonium fluoride solution (1mL) was added and the mixture was heated at reflux for an additional 12h. The resulting colorless solution was cooled and diluted with ether (100mL). This solution was

washed with 1M sodium hydroxide (3 x 50mL) and water (2 x 50mL), dried over magnesium sulfate, filtered, and evaporated to give ca. 45mL of a colorless oil. Vacuum distillation gave 17.9g (39%) of **54** as a colorless oil: bp184°C @ 0.018mm/Hg (lit.[27] 170-175°C @ 0.01mm/Hg); IR (film) 3060, 3030, 2980, 2930, 1740, 1585, 1485, 1370, 1020cm^{-1}; ^{1}H NMR (400MHz, $CDCl_3$) δ 7.35-7.17 (10H, m), 4.71 (1H, d, J=11.7), 4.47 (1H, d, J=11.7), 4.15 (2H, q, J=7.2), 4.07 (1H, dd, J=5.2, 7.2), 3.32 (1H, dd, J=13.7, 5.2), 3.23 (1H, dd, J=7.2, 13.8), 1.25 (3H, t, J=7.1); ^{13}C NMR (20MHz, $CDCl_3$) δ 170.5, 137.2, 135.7, 129.8, 128.7, 128.1, 127.7, 127.6, 126.2, 77.3, 72.2, 60.5, 36.2, 13.5.

(*Z*)-2-Benzyloxy-3-phenylthioacrylic Acid N-Methyl Amide (48)

To an ice-cooled solution of **54** (17.2g, 54.4mmol) in carbon tetrachloride (100mL) was added N-chlorosuccinimide (8.00g, 59.8mmol) and the suspension was stirred at room temperature for 8h, at which time a white solid floated on the surface. This mixture was filtered and the solvent was evaporated. The residue was dissolved in chloroform (50mL) and, after the addition of triethylamine (6.6g, 9.1mL, 65.3mmol), the mixture was heated at reflux for 1h. To the resultant dark-brown solution was added water (100mL) and the ice-cooled mixture was acidified to pH 1 with concentrated hydrochloric acid. This mixture was extracted with chloroform (3 x 50mL) and the combined extracts were washed with saturated aqueous sodium bicarbonate (50mL), dried over magnesium sulfate, filtered, and evaporated to give a yellow oil. This oil was filtered through silica (elution with 10% ethyl acetate-hexanes) and the solvent was evaporated. The residue was dissolved in a solution of methylamine in methanol (60%, 75mL) and stirred overnight at room temperature. Evaporation, followed by filtration through silica (elution with 1:1 ethyl acetate-hexanes) and then evaporation of the solvent, gave a light yellow oil. Crystallization of this material from ethyl acetate-hexanes afforded 10.6g (65%) of **48** as a white

crystalline solid: mp 53.5-55°C(lit.[27] 53-54°C); ^{1}H NMR (400MHz, $CDCl_3$) δ 7.46-7.24 (11H, m), 6.40 (1H, bs), 5.00 (2H, s), 2.79 (3H, d, J=5.17); ^{13}C NMR (20MHz, $CDCl_3$) δ 162.9, 145.4, 136.5, 134.1, 130.1, 129.3, 128.7, 128.6, 128.4, 127.5, 120.3, 73.6, 25.6.

(Z)-N-Methyl-5,6-O-(1-methylethylidene)-3-S-phenyl-2-O-(phenylmethyl)-3-thio-D-erythro-hex-2-enonamide (55)

To a stirred solution of diisopropylamine (0.87g, 1.20mL, 8.59mmol) in 20% hexamethylphosphoramide/tetrahydrofuran (25mL) at -78°C was added a 1.6M solution of n-butyllithium in hexanes (5.1mL, 8.22mmol) and the resulting solution was stirred for 20min. at 0°C and then cooled to -78°C. A solution of **48** (1.11g, 3.73mmol) in tetrahydrofuran (10mL) was added and the mixture was stirred at -78°C for 2h to give an opaque yellow suspension. A solution of **3** (0.486g, 3.73mmol) in tetrahydrofuran (10mL) was then added and the reaction mixture was allowed to warm to 0°C over about 2h, becoming clear at -50°C. Upon reaching 0°C the reaction mixture was quenched by the addition of saturated aqueous ammonium chloride (20mL) and diluted with ether (50mL). The layers were separated and the organic phase was washed with water (3 x 25mL), dried over sodium sulfate, filtered, and evaporated to give 1.64g of an amber oil. Flash chromatography of this oil on silica (1:1 ethyl acetate-hexanes) gave 0.949g (59%) of **55** as a white crystalline solid which was recrystallized from methylene chloride/hexanes to give needles: mp105.5-106°C; $[\alpha]_D$ -141° (c 3.1, $CHCl_3$); IR (film) 3320, 3060, 2940, 1655, 1382, 1370cm^{-1}; ^{1}H NMR (400MHz, $CDCl_3$) δ 7.45-7.26 (10H, m), 6.77 (1H, br d, J=4.8), 6.20 (1H, d, J=11.0), 5.02 (1H, d, J=11.0), 4.75 (1H, d, J=11.0), 4.37 (1H, dd, J=5.2, 14.1), 4.09 (1H, m), 3.91 (1H, dd, J=5.2, 8.8), 2.82 (3H, d, J=4.8), 1.37 (3H, s), 1.30 (3H, s); ^{13}C NMR (100MHz, $CDCl_3$) δ 164.4, 146.1, 136.1, 133.5, 131.3, 129.2, 128.6, 128.51, 128.5, 128.2, 127.5, 109.6, 77.6, 73.3, 72.3, 68.0, 26.7, 26.1,

25.3; MS *m/z* 429(M+), 383, 280, 238, 101, 91; Anal. Calcd for $C_{23}H_{27}NO_5S$: C, 64.31; H, 6.34; N, 3.26; S, 7.46. Found: C, 64.27; H, 6.18; N, 3.47; S, 7.58.

3-Phenylthiopropiolic Acid N-methylamide (58)

To a solution of diisopropylamine (110μL, 78mg, 0.77mmol) in tetrahydrofuran (10mL) at -78°C was added a 1.5M solution of n-butyllithium in hexanes (0.50mL, 0.74mmol). The resulting solution was stirred at 0°C for 0.5h at 0°C and cooled to -78°C. A solution of **48** (100mg, 0.33mmol) in tetrahydrofuran (10mL) was added to the LDA solution. This mixture was stirred 0.5h at 0°C then cooled back to -78°C. Water (5mL) was added and the mixture was allowed to warm to 0°C. After neutralization with saturated aqueous ammonium chloride (5mL) the mixture was diluted with ether and the layers were separated. The ethereal phase was washed with water (4 x 25mL), dried over sodium sulfate, filtered, and evaporated to give 92mg of an amber oil. Flash chromatography on silica (25→50% ethyl acetate-hexanes) gave 55mg (88%) of **58** as a colorless oil: IR (film) 3260, 3050, 2930, 2140, 1660cm^{-1}; ^{1}H NMR (80MHz, $CDCl_3$) δ 7.5-7.2 (5H, m), 6.2 (1H, br s), 1.8 (3H, 2s).

α-(Phenylthio)methylene Oxazolidinone (57)

To a solution of diisopropylamine (0.533g, 0.74mL, 5.27mmol) in tetrahydrofuran (20mL) at -78°C was added a 1.5M solution of n-butyllithium in hexanes (3.5mL, 5.27mmol) and the solution was stirred at 0°C for 0.5h. Hexamethylphosphoramide (0.45g, 0.44mL, 2.51mmol) was added and the solution was cooled to -78°C. A solution of **48** (0.751g, 2.51mmol) in tetrahydrofuran (15mL) was then added and the reaction mixture was stirred at 0°C for 15min. This mixture was cooled to -78°C and a solution of freshly distilled glyceraldehyde acetonide (3) (0.326g, 2.51mmol) in tetrahydrofuran (10mL) was added. After stirring the solution for 1h at -78°C saturated aqueous ammonium chloride (10mL) was added and the

mixture was warmed to room temperature and was diluted with ether (50mL). The aqueous layer was removed and the organic phase was washed with water (3 x 25mL), dried over sodium sulfate, filtered, and evaporated to give 920mg of an amber oil. Flash chromatography of this oil on silica (25→50% ethyl acetate-hexanes) gave 453mg (56%) of **57** as a white crystalline solid: mp86-87°C; IR (film) 3017, 1667, 1583, 1384, 1375, 761cm^{-1}; ^{1}H NMR (400MHz, $CDCl_3$) δ 7.42-7.23 (5H, m), 6.25 (1H, s), 5.09 (1H, d, J=7.5), 4.14 (2H, m), 4.02 (1H, m), 3.10 (3H, s), 1.49 (3H, s), 1.37 (3H, s); ^{13}C NMR (100MHz, $CDCl_3$) δ 160.1, 142.9, 134.3, 129.5, 129.2, 127.2, 110.9, 100.2, 91.4, 78.3, 65.8, 28.2, 26.7, 25.1; MS *m/z* 321, 220, 109; Anal. Calcd for $C_{16}H_{19}NO_4S$: C, 59.79; H, 5.96; N, 4.36; S, 9.98. Found: C, 59.88; H, 5.94; N, 4.32; S, 9.96.

5,6-O-(1-methylethylidene)-3-S-phenyl-2-O-(phenylmethyl)-3-thio-D-γ-hex-2-enolactone (59)

A solution of **55** (21mg, 0.049mmol) in n-octane (5mL) was heated at reflux for 4h, then evaorated to dryness *in vacuo*. The resulting colorless oil was filtered through silica (elution with 1:1 ethyl acetate-hexanes) to give 16.5mg (87%) of **59** as a colorless oil: $[\alpha]_D$ -280°(c 2.2, $CHCl_3$); IR (film) 3060, 2980, 2930, 1765, 1625, 1380, 1370cm^{-1}; ^{1}H NMR (400MHz, $CDCl_3$) δ 7.30 (10H, m), 5.37 (1H, d, J=11.8), 5.23 (1H, d, J=11.8), 4.84 (1H, d, J=4.5), 4.11 (1H, m), 3.78 (1H, dd, J=8.9, 6.5), 3.53 (1H, dd, J=5.3, 8.9), 1.34 (1H, s), 1.30 (1H, s); ^{13}C NMR (100MHz, $CDCl_3$) δ 186.0, 141.8, 135.5, 134.5, 132.0, 129.8, 129.3, 128.5, 128.2, 128.0, 110.2, 77.8, 76.0, 72.0, 63.5, 25.8, 25.0; MS *m/z* 398(M+), 101, 91.

5,6-O-(1-methylethylidene)-2-O-(phenylmethyl)-D-γ-hex-2-enolactone (61)

A solution of **59** (0.80g, 2.0mmol), tri-n-butylstannane (1.1g, 1.0mL, 13.7mmol), and azobisisobutyronitrile (AIBN) in dry benzene (30mL) was heated at

reflux for 6h. The resulting solution was cooled, concentrated, and subjected directly to flash chromatogaphy on silica (10% ethyl acetate-hexanes) to give a colorless oil which crystallized on standing. This material was dissolved in *sym*-tetrachloroethane (50mL) and to the solution was added pyridine hydrobromide (0.58g, 3.62mmol). This mixture was stirred overnight at 85°C. The reaction mixture was cooled and shaken with water (50mL). The layers were separated and the aqueous phase was extracted with methylene chloride (2 x 50mL). The combined organic solutions were dried over sodium sulfate and concentrated. Purification by flash chromatography on silica (25→50% ethyl acetate-hexanes) gave 0.42g (79%) of **61** as a white crystalline solid: mp78.5-79°C(methylene chloride/hexanes); IR (film) 2980, 1763, 1648, 1380cm^{-1}; ^{1}H NMR (400MHz, $CDCl_3$) δ 7.36-7.25 (5H, m), 6.26 (1H, d, J=2.0), 5.03 (1H, d, J=11.8), 4.98 (1H, d, J=11.8), 4.70 (1H, dd, J=2.0, 8.0), 4.09 (1H, dd, J=9.2, 6.2), 4.02 (1H, dd, J=9.2, 4.0), 3.85 (1H, m), 1.42 (3H, s), 1.33 (3H, s); ^{13}C NMR (100MHz, $CDCl_3$) δ 167.0, 146.6, 134.6, 128.7, 128.6, 127.6, 116.1, 110.2, 78.4, 72.9, 66.6, 26.7, 24.9; Anal. Calcd for $C_{16}H_{18}O_5$: C, 66.20; H, 6.25. Found: C, 66.28; H, 6.22.

5,6-O-(1-methylethylidene)-2-hydroxy-D-γ-hexanolactone (63)

A solution of **61** (121mg, 0.42mmol) in ethanol (3mL) was stirred for 1h with palladium hydroxide (53mg) under an atmosphere of hydrogen. The resulting mixture was filtered, concentrated, and subjected to flash chromatography on silica (1:1 ethyl acetate-hexanes) to give 74mg (88%) of **63** as a white crystalline solid: mp89-90°C (methylene chloride-hexanes); $[\alpha]_D$ -12.9°(c 2, $CHCl_3$); IR (film) 3400, 2980, 2930, 1785, 1380, 1370cm^{-1}; ^{1}H NMR (400MHz, $CDCl_3$) δ 4.56 (1H, ddd, J=4.0, 9.7, 9.7), 4.34 (1H, m), 4.21 (1H, m), 4.15 (1H, dd, J=6.3, 8.8), 3.91 (1H, dd, J=4.6, 8.8), 3.65 (1H, br d, J=4.0), 2.75 (1H, m), 2.11 (1H, m), 1.45 (3H, s), 1.37 (3H,

s); ^{13}C NMR (100MHz, $CDCl_3$) δ 177.0, 110.3, 76.6, 76.5, 67.9, 66.3, 33.3, 26.5, 24.9. Anal. Calcd for $C_9H_{14}O_5$: C, 53.46; H, 6.98. Found: C, 53.59; H, 7.02.

5,6-O-(1-methylethylidene)-2-methanesulfonyloxy-D-γ-hexanolactone (67)

To a solution of the alcohol **63** (134mg, 0.664mmol) and triethylamine (1mL) in methylene chloride (10mL) at 0°C was added methanesulfonyl chloride (152mg, 103μL, 1.33mmol) and 4-(dimethylamino)pyridine (cat.) with stirring. After 0.5h water (10mL) was added. The layers were separated and the aqueous layer was extracted with methylene chloride (2 x 20mL). The combined organic extracts were dried over magnesium sulfate and evaporated. The residue was purified by flash chromatography on silica (1:1 ethyl acetate-hexanes) to give 181mg (97%) of **67** as a white solid: $[\alpha]_D$ -8.75°(c 2, acetone); IR (film) 3021, 2993, 1800, 1375cm^{-1}; ^1H NMR (400MHz, $CDCl_3$) δ 5.38 (1H, dd, J=9.2, 10.0), 4.38 (1H, ddd, J=6.0, 6.4, 9.6), 4.24-4.13 (2H, m), 3.91 (1H, dd, J=8.7, 4.4), 3.28 (3H, s), 2.90 (1H, m), 2.41 (1H, ddd, J=9.6, 9.6, 13.3), 1.45 (3H, s), 1.36 (3H, s); ^{13}C NMR (20MHz, $CDCl_3$) δ 170.7, 110.5, 76.6, 76.3, 73.6, 66.3, 39.8, 31.7, 26.6, 24.9.

5,6-Ω-(1-methylethylidene) Leptosphaerin (70)

To a solution of **67** (98mg, 0.35mmol) in absolute ethanol (10mL) was added sodium azide (68mg, 1.05mmol) and the mixture was heated at reflux for 24h. The resulting solution was evaporated to dryness and the residue was dissolved in methylene chloride (15mL). The stirred solution was cooled to 0°C and to it were added triethylamine (360mg, 0.5mL, 3.6mmol), acetic anhydride (91mg, 84μL, 0.89mmol), and 4-(dimethylamino)pyridine (cat.). After stirring 1h at 0°C and 2h at room temperature, water (20mL) was added and the layers were separated. The aqueous layer was extracted with methylene chloride (2 x 20mL) and the combined organic fractions were dried over sodium sulfate and evaporated to give 123mg of a

colorless oil. Flash chromatography of this oil on silica (1:1 ethyl acetate-hexanes) gave 57mg (68%) of **70** as a white crystalline solid: mp128-129°C(methylene chloride-hexanes); $[\alpha]_D$ -57.3° (c 4, $CHCl_3$); IR (film) 3400, 2980, 2940, 1760, 1710, 1660, 1380, 1375cm^{-1}; ^1H NMR (400MHz, $CDCl_3$) δ 7.66 (1H, br s), 7.56 (1H, d, J=1.8), 4.92 (1H, dd, J=1.8, 6.9), 4.14-4.10 (1H, m), 4.03-3.98 (2H, m), 2.20 (3H, s), 1.46 (3H, s), 1.34 (3H, s); ^{13}C NMR (100MHz, $CDCl_3$) δ 169.7, 169.3, 127.5, 126.8, 110.7, 81.7, 76.6, 66.4, 26.7, 25.1, 23.6; MS *m/z* 184, 101; Anal. Calcd for $C_{11}H_{15}NO_5$: C, 54.77; H, 6.27; N, 5.81. Found: C, 54.78; H, 6.30; N, 5.86.

Leptosphaerin (2)

To a solution of leptosphaerin acetonide **70** (10mg, 0.04mmol) in tetrahydrofuran (2mL) at 0°C was added 1N hydrochloric acid (2mL) with stirring. After 1h at this temperature the reaction mixture was stirred overnight at room temperature. The resulting mixture was evaporated to dryness and the residue was dissolved in methanol (1mL). This solution was filtered through silica (elution with ethyl acetate) to give 8mg (ca. 100%) of 2 as a colorless oil, which crystallized after flash chromatography on silica (3:1 ethyl acetate-hexanes): mp185-187°C(lit.[6] 189.5-190.5°C): $[\alpha]_D$ +40° (c 0.2, H_2O); ^1H NMR (400MHz, acetone-d_6) δ 7.46 (1H, d, J=1.95), 5.06 (1H, dd, J=1.95, 5.60), 4.23 (1H, ddd, J=6.60, 4.23, 5.60), 4.13 (1H, dd, J=8.92, 6.60), 3.94 (1H, dd, J=4.23, 8.92), 2.18 (3H, s); ^{13}C NMR (100MHz, acetone-d_6) δ 170.1, 169.5, 128.0, 127.0, 81.9, 76.8, 66.1, 23.2.

I-D. References

1. Halstead, B.W. *Poisonous and Venomous Marine Animals*; vols. I and II. Washington: U.S. Government Printing Office, 1965.
2. Sondhiemer, E. and Simeone, J.B., Eds. *Chemical Ecology*. New York: Academic Press, 1970.
3. Seltzer, R.J. *Chem. Eng. News* **Dec. 16, 1674**, 20.
4. Miller, N.W. *The Pfizer Handbook of Microbial Metabolites*. New York: McGraw-Hill, 1961.
5. Johnson, T.W.Jr. and Sparrow, F.K.Jr. *Fungi In Oceans and Estuaries*. Weinheim: J. Cramer, 1961.
6. a. Schiehser, G.A. *PhD. Thesis*; Oregon State University, 1980.
   b. Schiehser, G.A.; White, J.D.; Matsumoto, G.; Pezzanite, J.O.; Clardy, J. *Tetrahedron Lett.* **1986**, *27*, 5587.
7. Baer, E.; Fischer, H.O.L. *J. Biol. Chem.* **1936**, *128*, 463.
8. Jones, L.W.; Sneed, M.C. *J. Am. Chem. Soc.* **1917**, *39*, 674.
9. DeShong, P.; Dicken, C.M.; Leginus, J.M. Whittle, A.R. *J. Am. Chem. Soc.* **1984**, *106*, 5598.
10. Jeanloz, R.W., ed. *Chemistry of Amino Sugars*, vols. 1-2. New York: Academic Press, 1965, 1969.
11. Leptosphaerin crystallized with orthorhombic symmetry and lattice constants of a = 4.8917(9), b = 7.657(2), c = 24.119(3)Å. The systematic extinctions, crystal density, and presence of chirality were uniquely accommodated by space group $P2_12_12_1$ with one molecule forming the asymmetric unit. Full matrix least squares refinements with anisotropic heavy atoms and fixed, isotropic hydrogens converged to a standard crystallographic residual of 0.0815.
12. Pravdic, N.; Fletcher, H.G. *Carbohydr. Res.* **1971**, *19*, 339.

13. a. Poisel, H.; Schmidt, U. *Chem. Ber.* **1975**, *108*, 2547.

b. Poisel, H. *Angew. Chem., Int. Ed. Engl.* **1976**, *15*, 294.

c. Poisel, H. *Chem. Ber.* **1977**, *110*, 942.

14. Vasella, A.; Voeffray, R. *Helv. Chim. Acta* **1982**, *65*, 1134.

15. Ireland, R.E.; Wilcox, C.S.; Thaisrivongs, S. *J. Org. Chem.* **1982**, *43*, 786.

16. Ballou, C.E. *J. Am. Chem. Soc.* **1957**, *79*, 165.

17. a. Brown, R.K.; Sharma, M. *Can. J. Chem.* **1966**, *44*, 2825.

b. Feast, A.A.; Overend, W.G.; Williams, N.R. *J. Chem. Soc.* **1965**, 7378.

c. Helferich, B.; Himmen, E. *Chem. Ber.* **1928**, *61*, 1825.

18. Since that time a new synthesis of such a compound has appeared:

Danishefsky, S.; Bednarski, M. *Tetrahedron Lett.* **1985**, *29*, 4311.

19. Fraser-Reid, B.; Hicks, D.R. *Can. J. Chem.* **1975**, *53*, 2017.

20. Kagan, H.B.; Girard, P.; Namy, J.L. *J. Am. Chem. Soc.* **1980**, *102*, 2693.

21. Richtmeyer, N.K. *Methods Carbohydr. Chem.* **1962**, *1*, 107.

22. a. Kornblum, N.; Frazier, H.W. *J. Am. Chem. Soc.* **1966**, *88*, 865.

b. Tschaen, D.M.; Turos, E.; Weinreb, S.M. *J. Org. Chem.* **1984**, *49*, 5058.

23. Thompson, W.J.; Horne, D.; Gaudino, J. *Tetrahedron Lett.* **1984**, *25*, 3520.

24. Nicolaou, K.C.; Pavia, M.R.; Seitz, S.P. *J. Am. Chem. Soc.* **1982**, *104*, 2027.

25. A preliminary account of this work has appeared: Pallenberg, A.J.; White, J.D. *Tetrahedron Lett.* **1986**, *27*, 5591.

26. Schmidt, R.R.; Betz, R. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 430.

27. Wermuth, C.-G.; Marx, H. *Bull. Soc. Chem. Fr.* **1964**, 732.

28. Betz, R. Dr. ver. nat. Dissertation, Universität Konstanz, 1984.

29. a. Ahn, N.T. *Top. Current Chem.* **1980**, *88*, 145.

b. Felkin, H.; Charest, M.; Prudent, N. *Tetrahedron Lett.* **1968**, 2199.

For discussion of the case involving α-alkoxyaldehydes see:

c. Evans, D.A.; Nelson, J.V.; Taber, T.R. *Top. Stereochem.* **1982**, *13*, 1.

d. Mulzer, J. *Nachr. Chem. Tech. Lab.* **1984**, *32*, 16.

30. Hein, S.J.; Keszler, D.A. *Acta Cryst.* **1987**, *C43*, 2457. This material crystallized with monclinic symmetry and lattice constants of a = 12.524(4), b = 7.938(2), c = 11.933(2)Å. The systematic absences uniquely determined space group C^2_2-P^2_1. The positions of eleven non-hydrogen atoms were determined by direct methods. The remaining non-hydrogen atoms were located with DIRDIF-strengthened Fourier techniques, which, with fixed isotropic hydrogen atoms, gave $R(F_0) = 0.039$.

31. Schmidt, R.R.; Speer, H. *Synthesis*, **1977**, 869.

32. Seyferth, D. *J. Am. Chem. Soc.* **1957**, *79*, 2133.

33. Badger, R.A.; White, J.D. unpublished results.

34. Kraatz, U.; Hasenbrink, W.; Wamhoff, H.; Korte, F. *Chem. Ber.* **1971**, *104*, 2458.

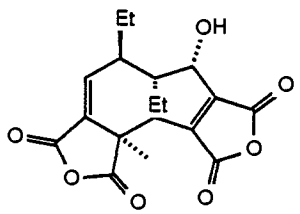
35. Rollin, P. *Tetrahedron Lett.* **1987**, *28*, 3813.

36. Still, W.C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

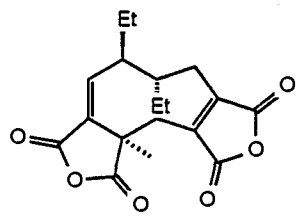
Part II: Approaches to the Synthesis of Byssochlamic Acid

II-A. Introduction.

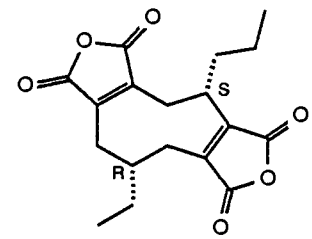
The first members of the series of fungal metabolites that became known as nonadrides were isolated as far back as the 1930's.[1] Glauconic and glaucanic acids (**1** and **2** respectively) were isolated by Wijkman in 1931[2] from *Penicillium glaucum* and



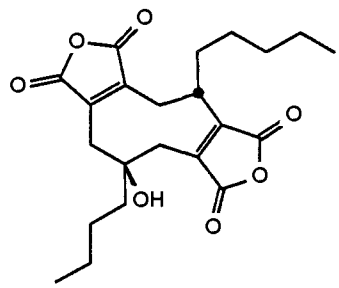
Glauconic Acid **1**



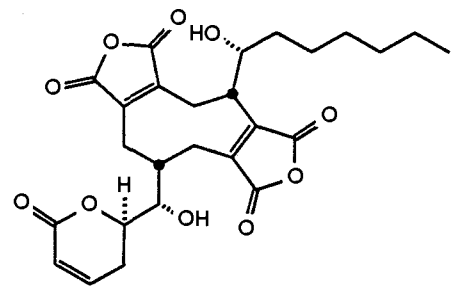
Glaucanic Acid **2**



Byssochlamic Acid **3**



Scytaldin **4**



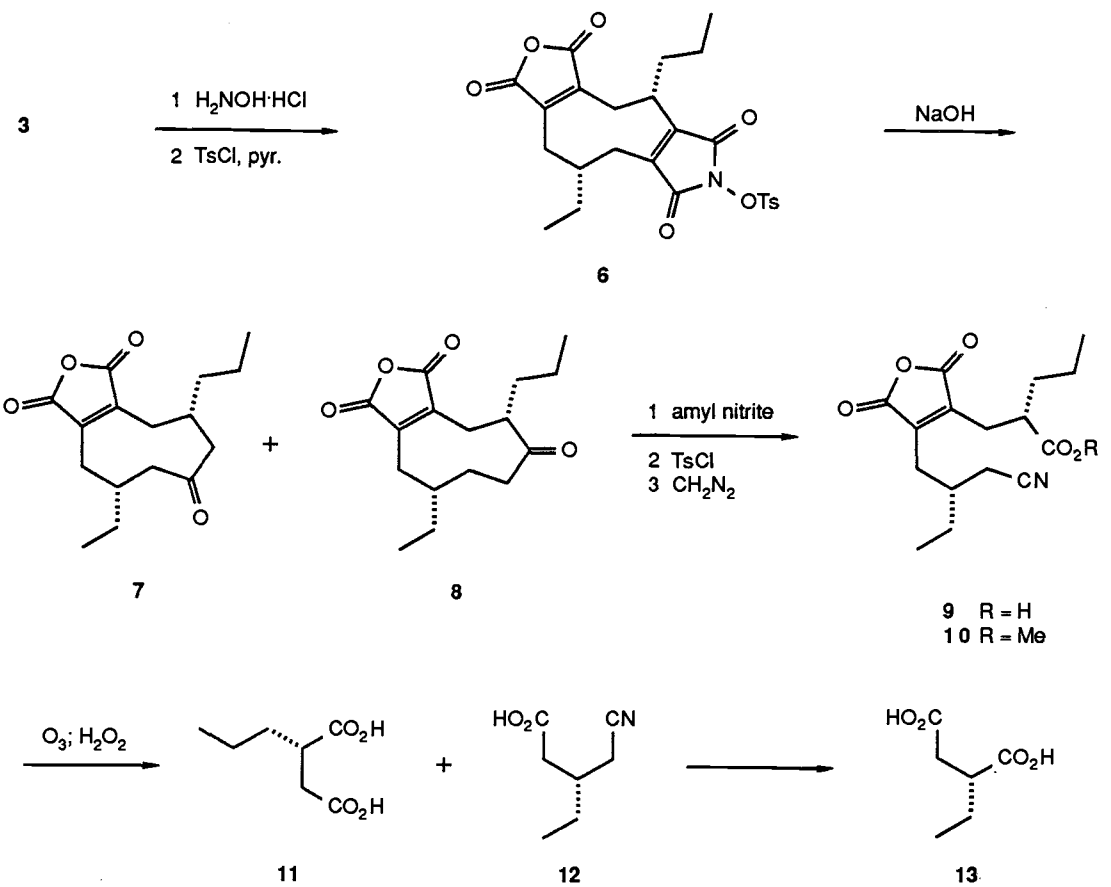
Rubratoxin B **5**

by Yuill[3] in 1934 from *Penicillium purpurogenum* . A third nonadride, byssochlamic acid (**3**), was obtained in 1933 by Raistrick and Smith[4] from *Byssochlamys fulva*, an ascomycete known to be responsible for spoilage of canned fruits[5] and vegetables.[6] The genus *Byssochlamys*, first encountered in the early years of this century, is characterized by its stern resistance to the usual methods of sterilization such as heat and alcohol. Although little is known about the toxicity of byssochlamic acid itself, related compounds such as rubratoxin B (**5**) are associated with liver damage in animals[7] and

man.[8] The structural hardiness of the nonadrides, coupled with their toxicity and widespread occurrence in soil, give the organisms great economic importance.

For a number of years the exact structures of these materials remained elusive, despite extensive chemical investigation on the part of Wijkman and coworkers.[9] A solution to the structure problem of byssochlamic acid was first proposed by Barton, Sutherland, and Baldwin[10] and later confirmed by X-ray crystallography.[11] The absolute stereochemistry of byssochlamic acid was established largely on the basis of further study by Barton and coworkers.[12]

The free tetracarboxylic acid was obtained by precipitation from aqueous culture of *B. fulva* by addition of mineral acid. This material titrates as a tetrabasic acid, which

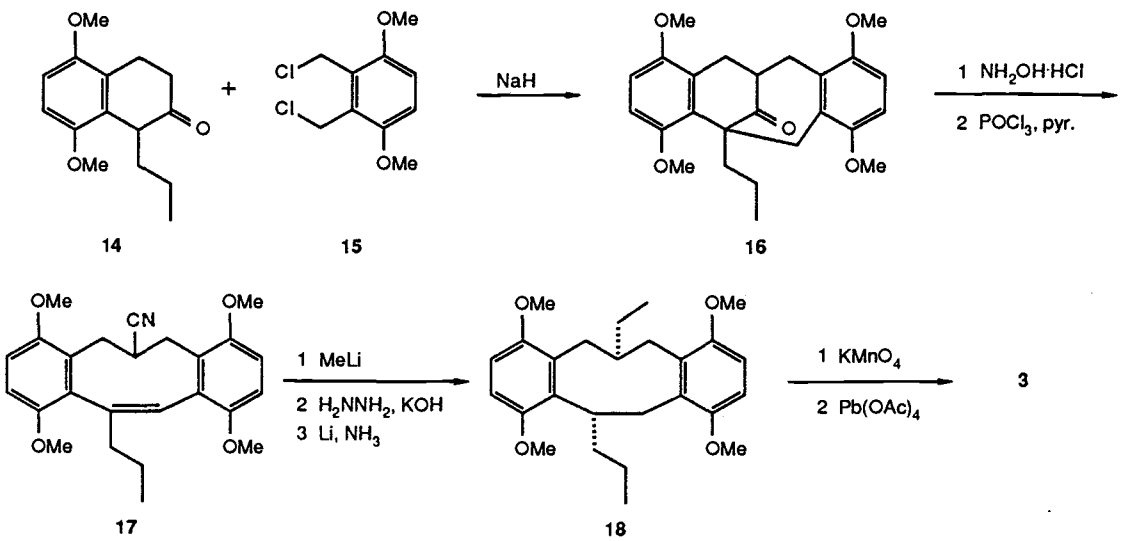


rapidly loses two molecules of water upon protonation to give a bis-anhydride. The structure of this anhydride was determined by degradation to compounds of known

structure. Thus, byssochlamic acid was treated with hydroxylamine hydrochloride, followed by *p* -toluenesulfonyl chloride, to give the activated N-hydroxyimide **6**. Hydrolysis with 1N sodium hydroxide gave a mixture of ketones **7** and **8** in 11 and 26% yield respectively from byssochlamic acid.

Ketone **8**, upon treatment with amyl nitrite and hydrochloric acid, gave an oxime which underwent a Beckmann fragmention on exposure to *p* -toluenesulfonyl chloride to afford nitrile acid **9**, isolated as its methyl ester **10**. Ozonolysis of **10** and oxidative workup with alkaline hydrogen peroxide gave the known acid **11**[13] and nitrile acid **12**. The latter was correlated with ethylsuccinic acid (**13**) of known absolute stereochemistry[14] by Hofmann rearrangement and oxidation.

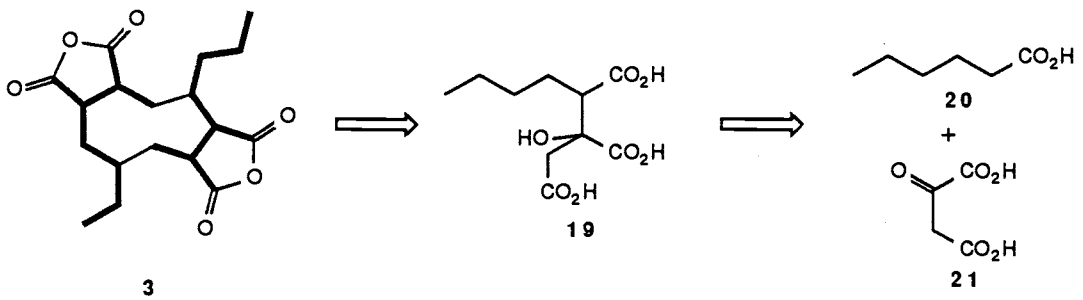
The first, and thus far only, synthesis reported for any nonadride is Stork's preparation of byssochlamic acid.[15] In this work Stork sought to avoid manipulation of intermediates containing the reactive maleic anhydride moiety by introducing these late in the synthesis. For this reason the bishydroquinone dimethyl ether **18**, in which the



aromatic rings act as latent anhydrides, was Stork's key intermediate. This material was converted to byssochlamic acid by oxidation with potassium permanganate, followed by lead tetraacetate, in 13% yield from **18**. Compound **18** was obtained by a sequence

beginning with condensation of **14** with **15**. Oxime formation, followed by fragmentation with phosphorus oxychloride, gave stilbene derivative **17**, which was converted to **18** by reductive alkylation and a dissolving metal reduction.

A biosynthesis has been proposed[16] in which the suggestion is made that byssochlamic and glauconic acids arise from differing dimerization modes of a common C9-unit. This unit, in turn, could be derived from a substituted citric acid **19** formed



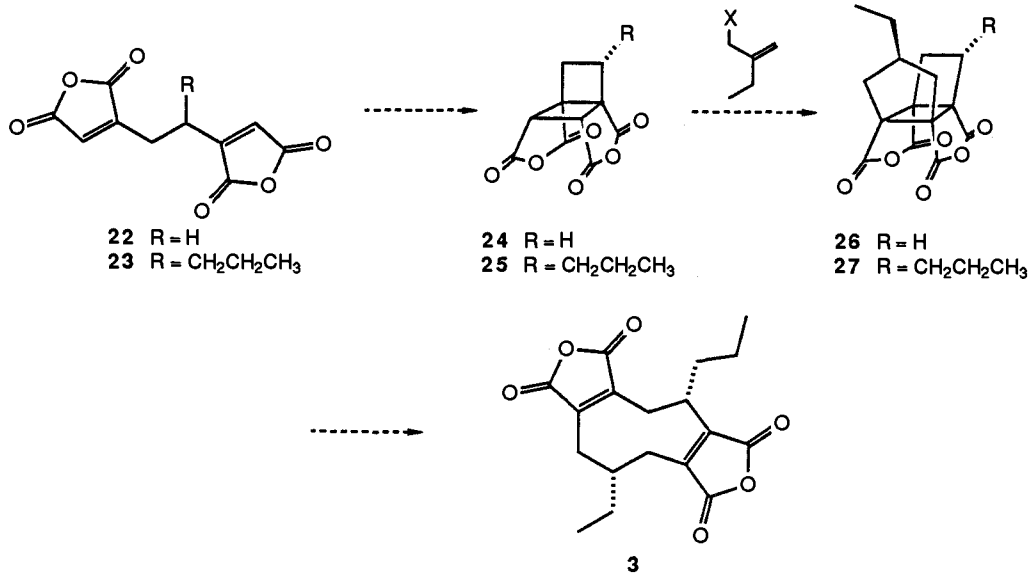
3 **19** **20** + **21**

by the condensation of hexanoate with oxaloacetate. Feeding experiments by Sutherland[17] in which isotopically labelled glucose, acetate, and pyruvate were fed to *Penicillium purpurogenum* have supported this idea in the case of glauconic acid, but the corresponding experiments with *Byssochlamys fulva* have not been reported.

In light of the biological significance of the nonadrides and of the dearth of synthetic effort in this area, we decided to undertake an investigation directed toward the synthesis of members of this class of compounds. It was our aim, in particular, to devise a concise and high yielding sequence leading to byssochlamic acid.

II-B. Discussion

Examination of the structure of byssochlamic acid reveals two isolated chiral centers located on a nine-membered ring. Fused to this ring are the characteristic maleic anhydride moieties unique to this class of natural products. In planning a synthetic entry to this system we sought a succinct method that would allow establishment of



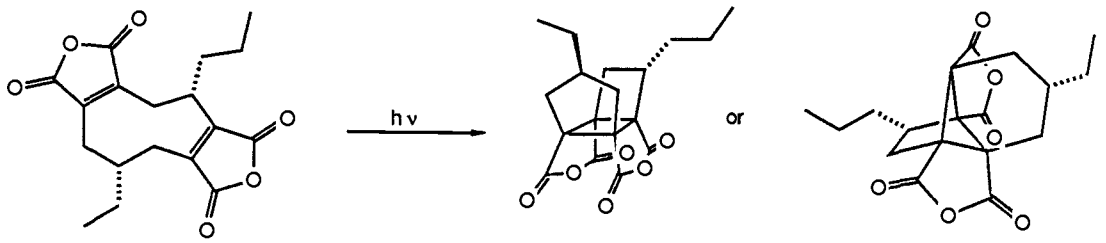
Scheme 1

these structural elements in a regio and stereo defined way. Based on this philosophy we first elected to explore the approach shown in Scheme 1.

An appropriate 1,5-hexadiene derivative **23** could undergo [2+2] photocycloaddition to give a bicyclo[2.2.0]hexane **25**, to which could be annulated a three-carbon segment to give the pentacyclic intermediate **27**. A thermal retrocyclization [2+2] would then release byssochlamic acid (**3**) in which the configuration at the stereocenters has been determined by the steric congestion of the endo face of **25** and **27**. Maleic anhydride itself is known[18] to dimerize in moderate yield in an intermolecular example of the first step of this sequence. In what is apparently the

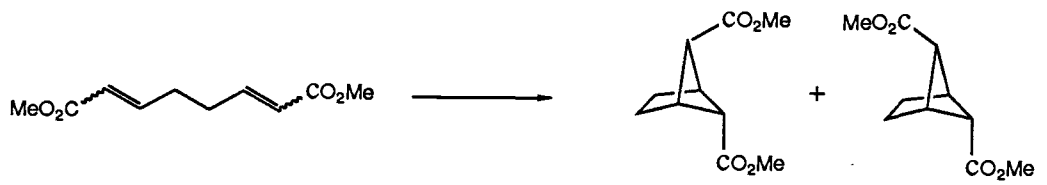
reverse of the process we envisioned, Barton[12] observed that byssochlamic acid could be photolyzed to give a saturated product found to be either **27** or **28**.

In general, there are two modes of intramolecular addition for a 1,5-diene



3 **27** **28**

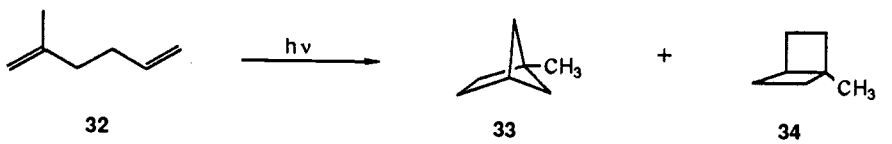
leading to either the bicyclo[2.2.0] or the bicyclo[2.1.1]hexane ring systems. The regiochemistry observed seems to depend upon various factors including the nature and



29 **30** **31**

degree of substitution.[19] In the (sensitized) cycloaddition of all three isomeric 1,5-hexadienes **29** the "crossed" regiochemistry prevails[20] to afford the bicyclo[2.1.1]hexanes **30** and **31** in the ratio 65:35 and high overall yield. However, under certain circumstances the desired bicyclo[2.2.0]hexane structure is obtained[19] as in the formation of **34** from **32** observed by Srinivasan.

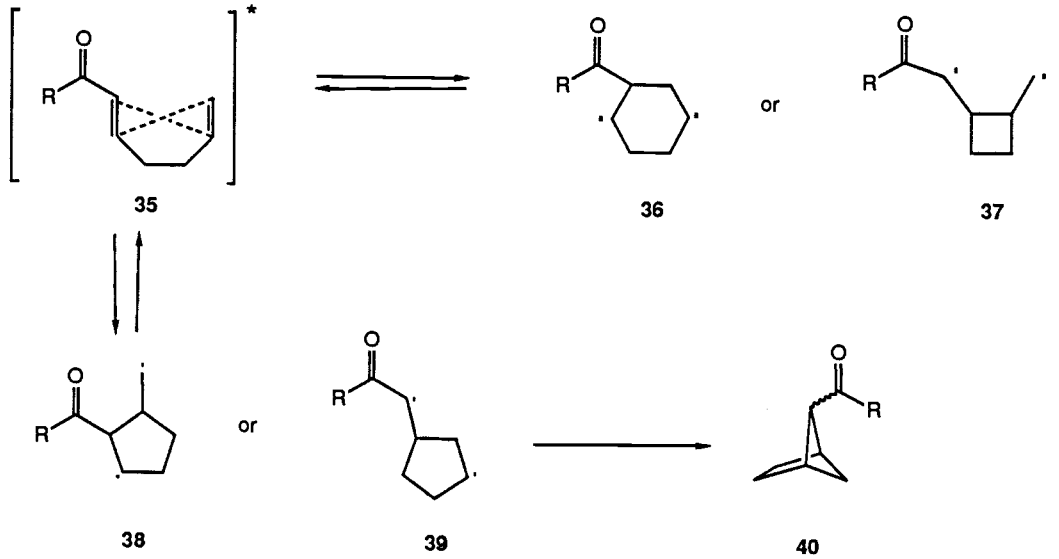
In the irradiation of a diene such as **35** the n-π* transition first produces an excited singlet species. This can give a triplet either through intersystem crossing or by



32 **33** **34**

the use of a triplet sensitizer in the irradiation. This excited triplet yields a triplet diradical **38** or **39** (**36** and **37** simply return to **35**) which each give the same product

40. This tendency of many sensitized photolyses to give the "crossed" products has been articulated as "the rule of the five"[21] which states that the first-formed diradicals in sensitized irradiations are generally those containing a five-membered ring. Thus the

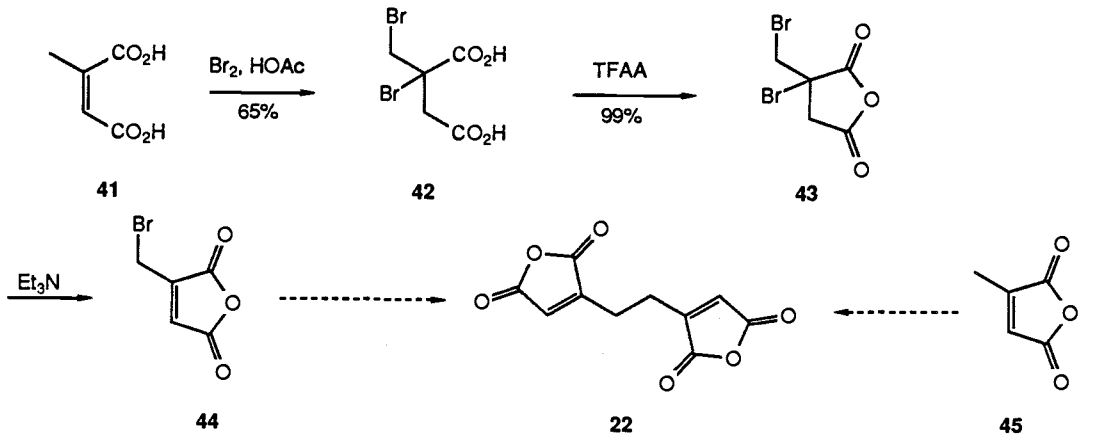


synthetic challenge became to find circumstances under which the rule of the five could be violated or conditions under which a direct irradiation could be effected.

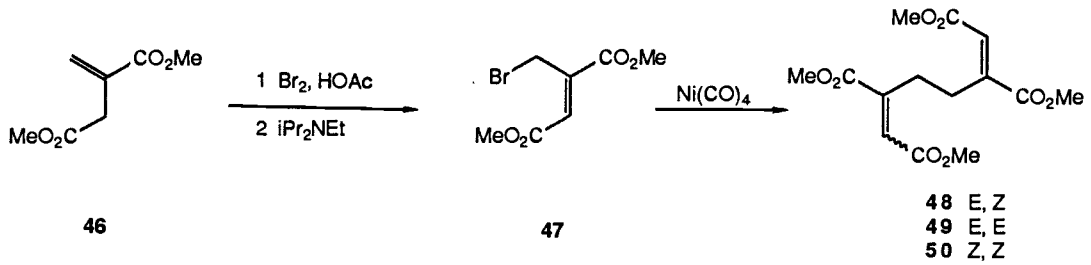
Our first attempt at executing this strategy centered on the preparation of compound **22** in which the necessary anhydride rings were present. Self-coupling of an allylic bromide such as **44** could conceivably lead to **22**. Bromide **44** was available (albeit in very low yield) by bromination of citraconic acid (**41**), dehydration, and dehydrobromination according to a known[22] procedure. However, attempts to couple this material using nickel carbonyl,[23] magnesium metal,[24] and samarium diiodide[25] led only to the formation of complex mixtures. Attempted alkylation of the enolate, prepared with lithium diisopropylamide, of citraconic anhydride[26] (**45**) with **44** also failed to afford the desired bis anhydride.

It is reasonable to suppose that **44** could undergo reaction along a multitude of pathways by virtue of the fact that each of the five centers in this molecule can function as an electrophile. On the premise that the anhydride functionality of **44** was simply too

reactive to permit the manipulations described above, we undertook the analogous

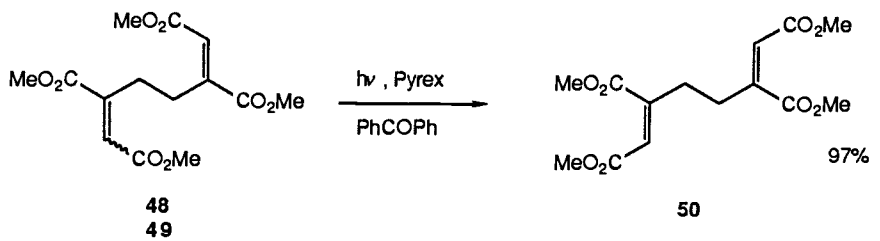


sequence beginning with dimethyl itaconate (**46**). This substance could be converted to the allylic bromide **47**[27] by bromination and subsequent elimination in a manner similar to that used to generate **44**. Again, attempts to couple this material by oxidation of the



homocuprate,[28] and by treatment with samarium diiodide led to intractable mixtures. However, treatment of **47** with nickel tetracarbonyl[29] gave an 83% yield of a mixture of diene isomers **48** and **49**[30] in the ratio 2:1.

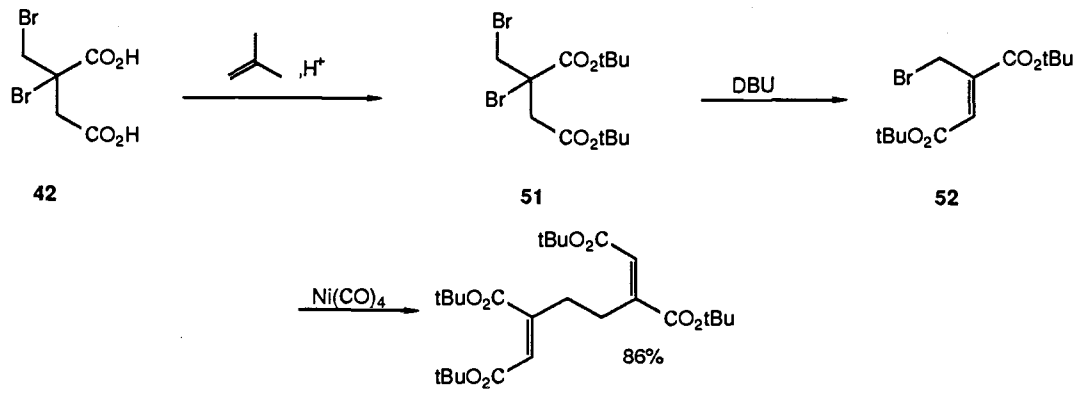
Photolysis of these dienes gave very clean conversion to the third (Z,Z) isomer



50 with no detectable formation of any cyclized products. Furthermore, attempts to introduce the required n-propyl group by deprotonation of **48** resulted only in

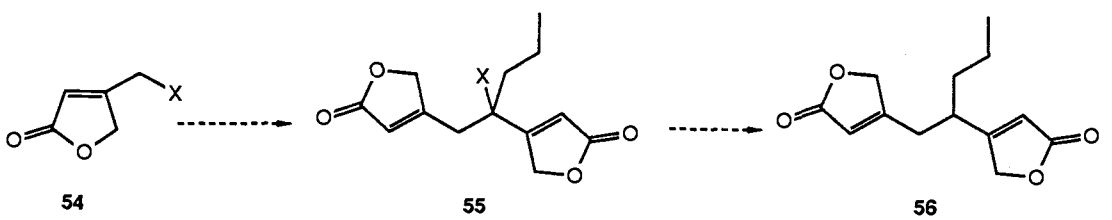
polymerization of the diene, probably via acylation of intermediate enolates. In an effort to avoid this behavior we sought a form of **48** in which the carbonyl groups were less reactive toward electrophilic reagents.

The corresponding tetrakis t-butyl ester **53** could be prepared in precisely the same manner as **48/49**. Allylic bromide **52**, prepared by reaction of **42** with isobutylene followed by dehydrobromination of diester **51**, underwent a clean coupling with nickel carbonyl to give **53** in 53% overall yield from **42**. In marked contrast to

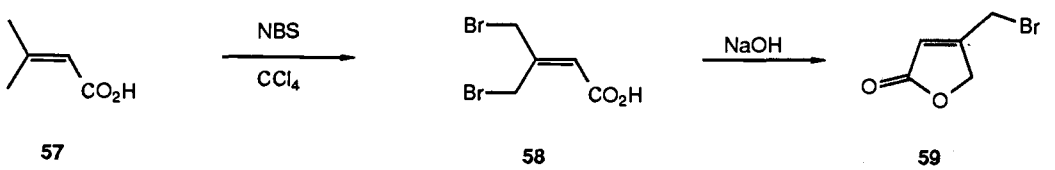


48, **53** gave no reaction upon treatment with base.

In a final variation on the use of a citraconate or related compound as starting

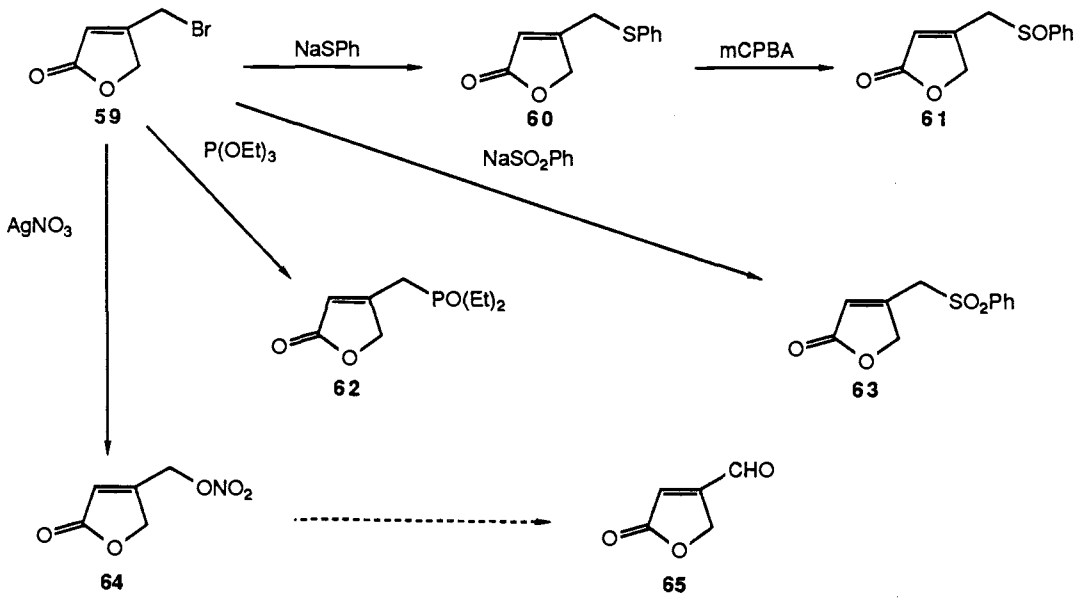


material we investigated several functionalized butenolides. These were materials



lacking one of the two carbonyl groups present in the anhydrides and were therefore

considered to be less prone to indiscriminate polymerization. Specifically, a lactone such as **54,** in which X is an activating group, could be alkylated sequentially with a halide like **44**, **47**, or **52** and with n-propyl bromide to produce the needed substrate for the photoaddition. Accordingly, bromide **59** was prepared by bromination[31] of senecioic acid (**57**) and lactonization with sodium hydroxide. Displacement of bromide

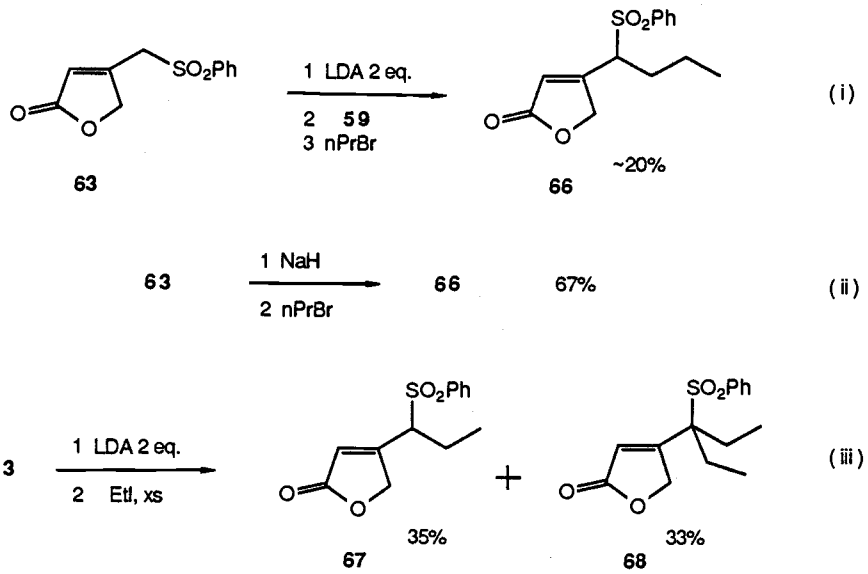


from **59** with sodium phenylthiolate gave **60**, which was oxidized to sulfoxide **61** with m-chloroperbenzoic acid in 66% yield from **59**. Unfortunately only complex mixtures were obtained when alkylation of the anion with **59** was attempted.

Phosphonate **62** is available[32] from **59** by Arbuzov reaction with triethylphosphite. Although alkylation of phosphonates is a well known reaction[33] proved to be unsuitable for alkylation with **59**, giving complex mixtures of products. Also available from **59** is nitrate **64**, by treatment of **59** with silver nitrate.[34] This intermediate was prepared with the intention of conversion to aldehyde **65**, but attempts to effect this outcome also met with failure.

Sulfone **63** derived from **59** by displacement with sodium phenylsulfinate[35] (82%) looked more promising, however. While attempted alkylation with **59** (lithium diisopropylamide, THF/HMPA) gave no reaction, alkylations with other alkylating

agents proved quite feasible. Deprotonation of **63** with two equivalents of lithium

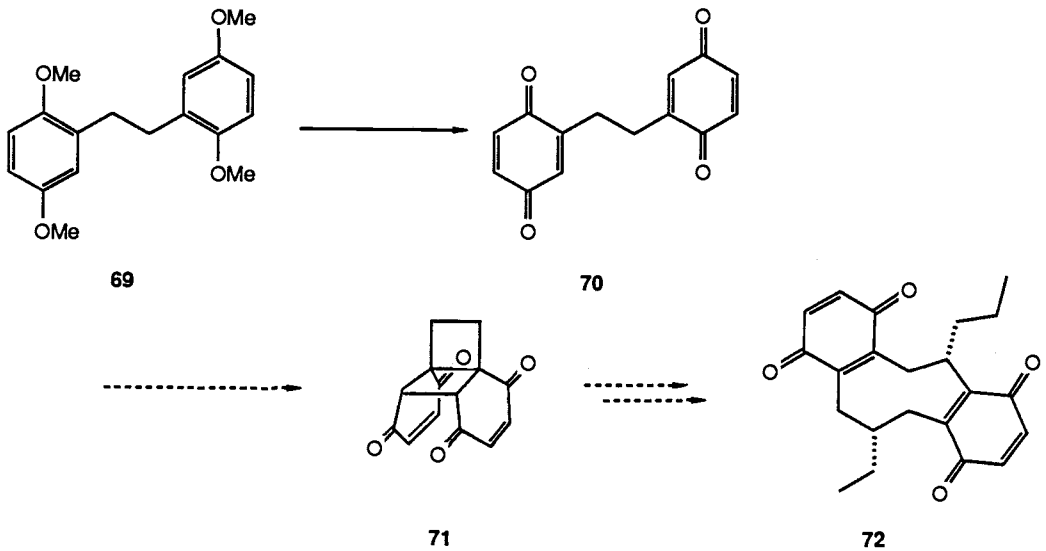


diisopropylamide and treatment with one equivalent of **59** followed by one equivalent of n-propyl bromide gave only a 20% yield of propylated sulfone **66** (equation i).

A series of alkylation experiments served to illuminate the situation obtaining with this system. Deprotonation of **63** with one equivalent of sodium hydride and subsequent treatment with n-propyl bromide gave **66** in 67% yield (equation ii). Somewhat disconcertingly, however, treatment of **63** with two equivalents of lithium diisopropylamide followed by an excess of ethyl iodide gave a good yield of a nearly equimolar mixture of mono- and dialkylated products **67** and **68** (equation iii).

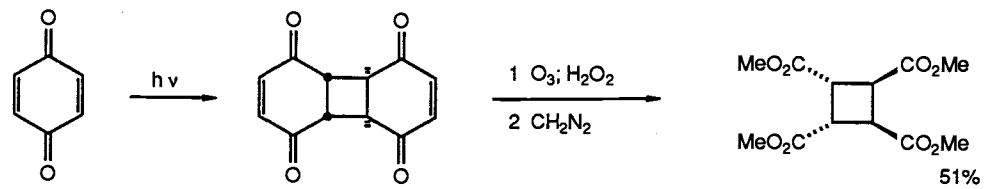
On the basis of the experiments described above it was decided that the butenolide alkylation approach was impracticable due to our inability to introduce the two required alkyl groups in a controlled fashion. For this reason we sought a new tactic which would allow us to circumvent this problem. In particular, we desired an accessible intermediate with the required substitution which was amenable to the planned photocyclization and from which the anhydride systems of byssochlamic acid could be generated.

Consistent with these objectives, we chose bibenzyl **69** is a simple example as our initial example. For this intermediate we envisioned preparation of bis quinone **70** and its photolysis/thermolysis in the same manner as that described above. The



69 **70** **71** **72**

photodimerization of benzoquinone derivatives as well as the subsequent oxidative

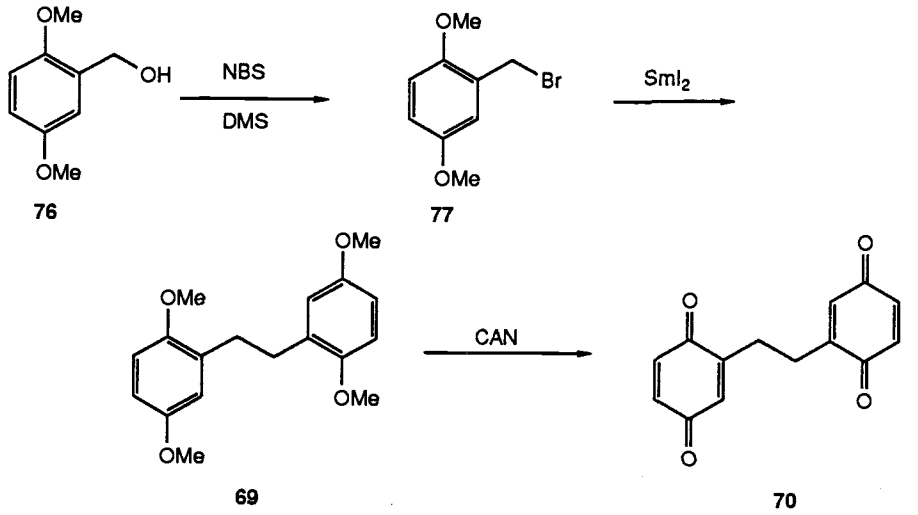


73 **74** **75**

degradation to cyclobutane **75** were reported by Gold and Ginsburg.[36] Furthermore, the method of oxidative cleavage put forward by these workers offered the promise of a considerably higher yield than that of Stork[17] in a similar situation.

We began the preparation of **70** with a Corey-Kim[37] bromination of commercially available 2,5-dimethoxybenzyl alcohol (**76**) which gave known bromide **77**[38] in good yield. Coupling of **77** with samarium diiodide[25] gave a quantitative yield of bibenzyl **69**.[24] Oxidative demethylation[39] of this intermediate gave a modest yield of unstable bis quinone **70**, photolysis of which gave only decomposition.

In spite of this unpromising result, it was decided to prepare the analogue of **67** incorporating the n-propyl group (**83**). Known ketone **79** was prepared by a Friedel-

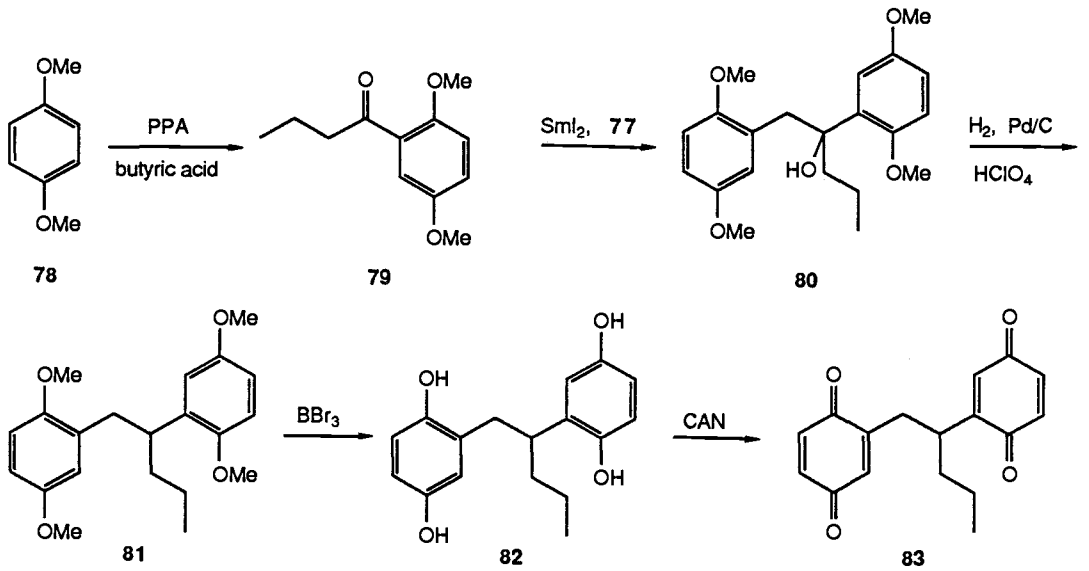


Crafts procedure[40] and alkylation of this ketone with **77** using samarium diiodide according to the procedure of Kagan[25] gave a tertiary alcohol **80**. This benzylic alcohol underwent hydrogenolysis to give a 67% yield of **81**. Although the oxidative demethylation procedure used in the preparation of **70** could be employed here, it was found that a much higher yield could be obtained by executing the transformations separately. Thus, demethylation[41] of **81** with boron tribromide and subsequent oxidation with ceric ammonium nitrate gave quinone **83** in 83% yield. Once again, however, photolysis gave complex mixtures of products. This was the case whether or not a sensitizer was used and regardless of the optical filters (Pyrex, Corex, Vycor, or quartz) employed.

The literature on quinone photodimerization suggests that the degree of alkyl substitution plays an important role in determining the success of these reactions. In particular, Cookson[42] stated that quinones bearing two alkyl groups in a 1,4 orientation appeared to be the best candidates for dimerization.

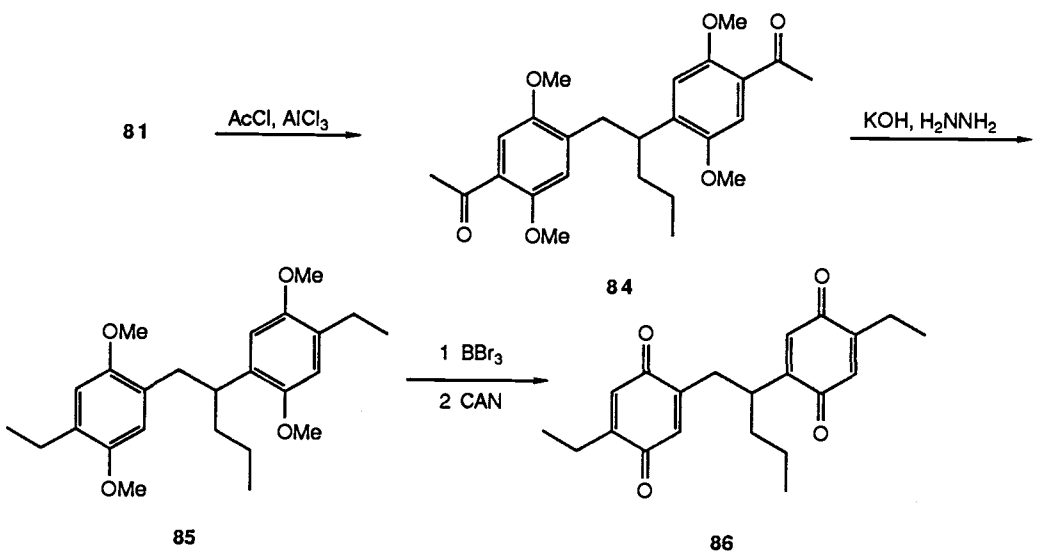
Accordingly, diethyl bis hydroquinone dimethyl ether **85** was prepared by Friedel-Crafts acylation of **81** followed by Wolff-Kischner reduction of the

intermediate diketone **84**. Deprotection and oxidation as described above gave a



quantitative yield of beautifully crystalline bis-quinone **86**. As before, however, photolyses of this material gave no useful products.

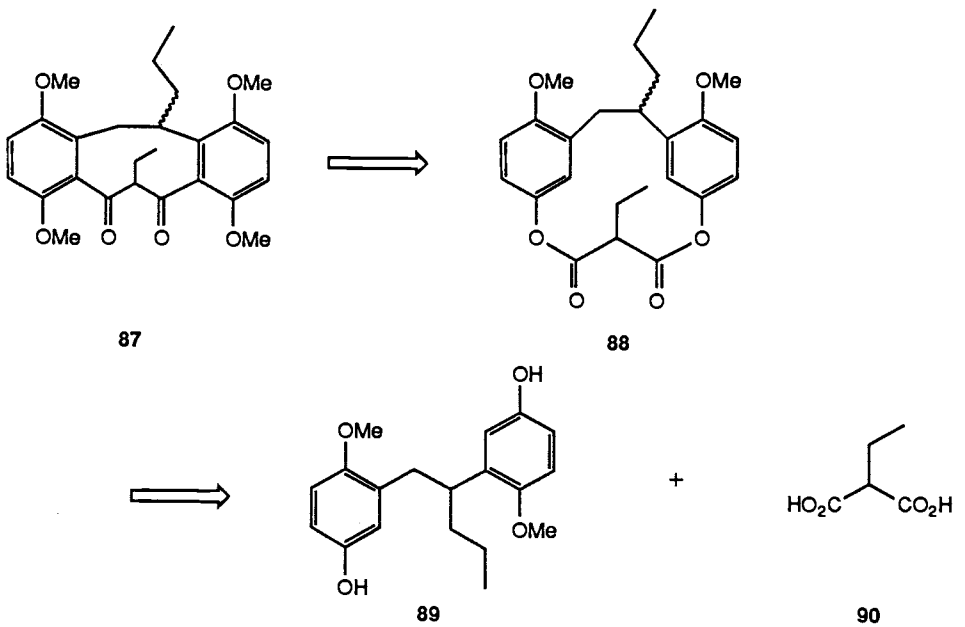
The setbacks suffered during attempts to develop a photochemically based route



to byssochlamic acid forced a reconsideration of the strategy envisioned in this approach. The studies described above clearly suggest that photochemical pathways of the type outlined are impracticable. For this reason we chose to explore a plan that avoided this photochemical strategy.

Our main goal, however, remained to find an expeditious means of generating a nine-membered ring intermediate such as **87**, from which one could obtain, by simple chemical transformations, byssochlamic acid. Because **87** is a bis O-alkoxy acetophenone derivative we foresaw the possibility of obtaining it via two Fries rearrangements from diester **88**. This plan could become a reality if a suitably protected derivative of **82**, such as **89**, could be cyclized with ethylmalonic acid **90** to afford **88**.

In order to accurately assess the feasibility of this idea a series of molecular



mechanics calculations were undertaken using the MMX-MODEL program. These calculations revealed several interesting pieces of information about byssochlamic acid (**3**), diester **88**, and diketone **87**.

By far the most important revelation was that at each of these three stages of the proposed synthesis the diastereomer opposite to that desired is the more stable. The calculated conformations of **87** and **88** are shown in Figures II.1 and II.2 respectively. The energy difference between the diastereomers varies with the compound in question. In the case of the diesters **88** the energy difference between epimers was predicted to be 10.8 kcal/mol. If equilibrium existed between these compounds one would expect to

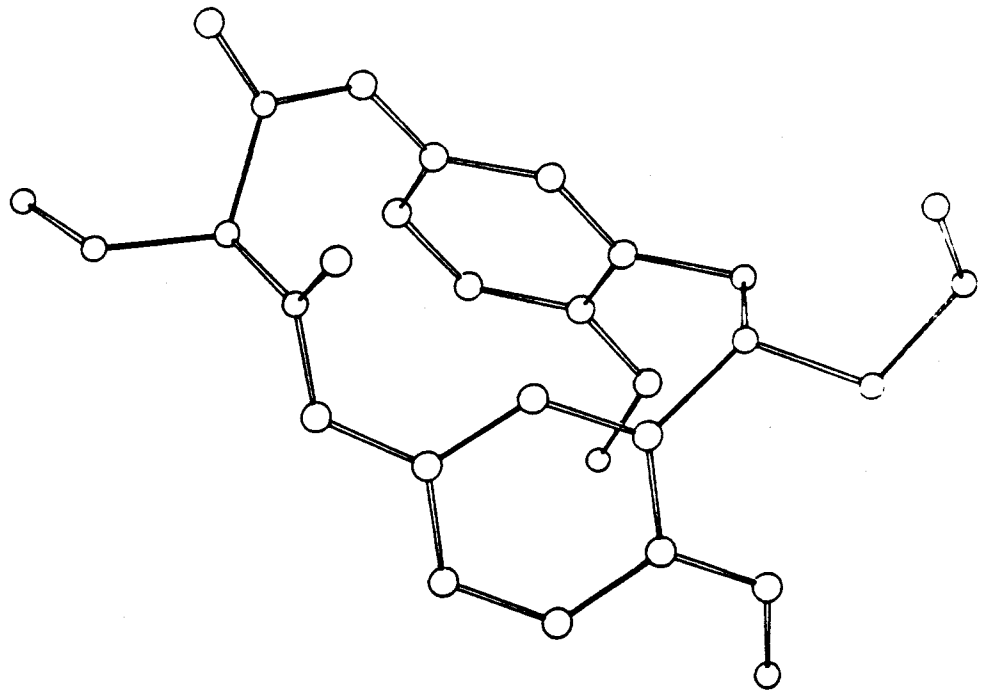


Figure II.1 ORTEP Plot of **88** from Molecular Mechanics Calculation

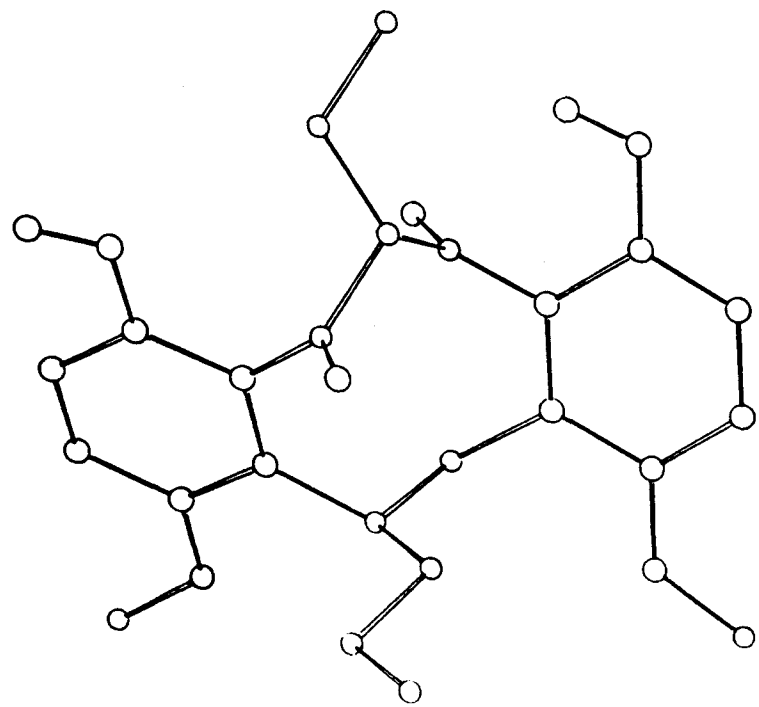
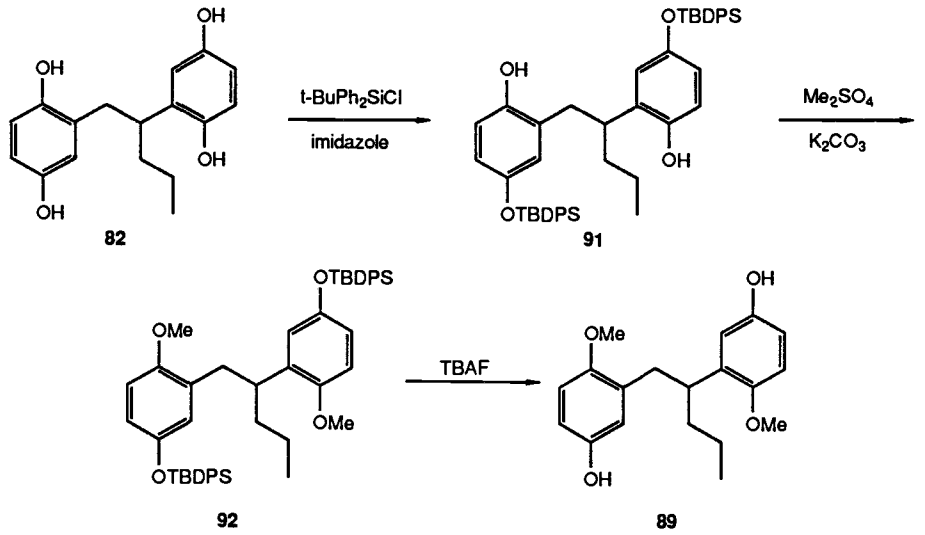
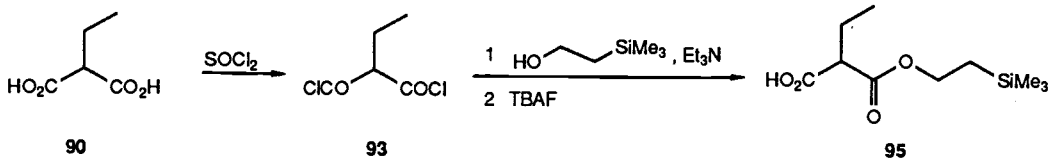
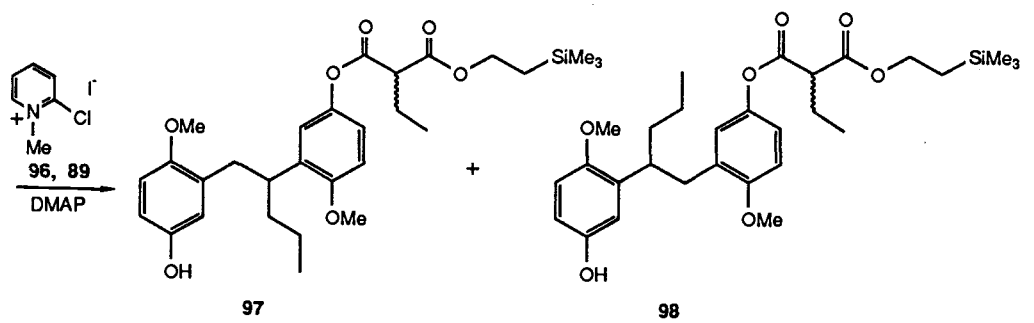
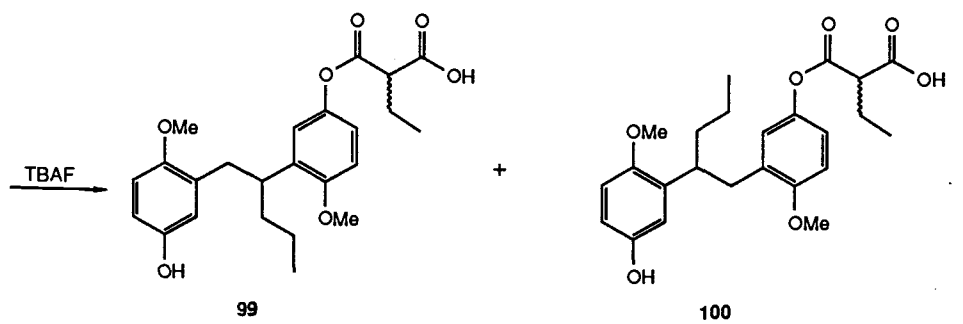


Figure II.2 ORTEP Plot of **87** from Molecular Mechanics Calculation.


OH
OH
OH
OH
82
t-BuPh2SiCl
imidazole
OTBDPS
OH
OH
OTBDPS
91
Me2SO4
K2CO3
OTBDPS
OMe
OMe
OTBDPS
92
TBAF
OH
OMe
OMe
OH
89


HO2C
CO2H
90
SOCl2
ClCO
COCl
93
1 HO SiMe3 , Et3N
2 TBAF
HO2C
O
O
SiMe3
O
95

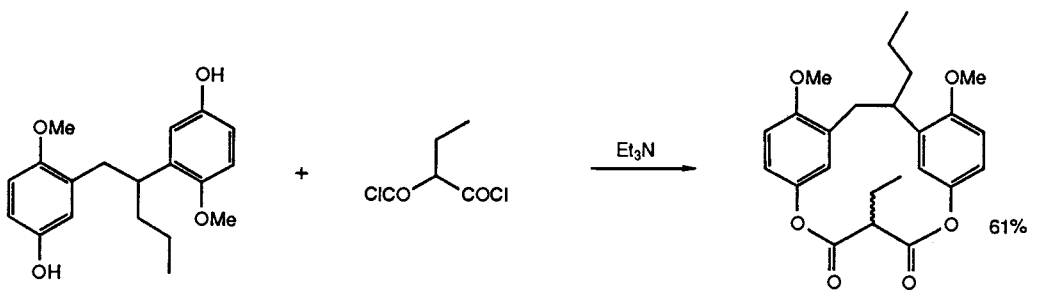

I-
+N
Cl
Me
96, 89
DMAP
OMe
OMe
OH
O
O
O
SiMe3
97
+
OMe
OMe
OH
O
O
O
SiMe3
98


TBAF
OMe
OMe
OH
O
O
O
OH
99
+
OMe
OMe
OH
O
O
O
OH
100

find very little, if any, of the less stable epimer. At the stage of the diketones **87** the epimers differ by only 3.3 kcal/mol - still leading one to expect exclusive formation of the undesired epimer. Interestingly, however, the epimers of byssochlamic acid itself apparently differ by only 0.5 kcal/mol with the epimer of the natural material giving the lower energy.

In an effort to test these predictions we undertook the preparation of **89**. It was found that, while reaction of **82** with t-butyldimethylsilyl chloride produced little selectivity between di- and trisilylation, the use of t-butyldiphenylsilyl chloride allowed procurement of a 52% yield of bis-silylated product **91**. Methylation with dimethyl sulfate in the presence of potassium carbonate gave the hydroquinone ether **92**, desilylation of which gave the desired bis-phenol **89**.

When an equimolar mixture of this phenol and ethylmalonic acid were subjected to the Mukaiyama esterification procedure (2-chloro-1-methylpyridinium iodide (**96**), triethylamine)[43] there was obtained a mixture of unidentifiable materials. Alternatively, ethylmalonyl dichloride[44] (**93**) could be converted via the corresponding diester **94** to monoester **95**, which, in turn, gave a mixture of esters **97** and **98** upon reaction with



89 93 88

89 and **96**. Deprotection of this pair of trimethylsilylethyl esters with fluoride gave the corresponding mixture of acids **99** and **100**. Attempts to lactonize this material by Mukaiyama's procedure met with failure as did the use of a modified version of this protocol.[45] However, the more direct expedient of reaction of **89** with ethylmalonyl

dichloride (**93**) at -78°C afforded a moderate yield of a material identified as macrolide **88**.

The assignment of structure to **88** rests on a combination of analytical data. In particular, the infrared spectrum of **88** shows a carbonyl frequency of 1770 cm^{-1}, consistent with an aryl ester, and the absence of a hydroxyl band. The ^{1}H NMR spectrum of this substance shows resonances at all of the characteristic frequencies of the bibenzyl system possessed by this series of compounds, all of which integrate to the expected values. The ^{13}C NMR spectrum of this material is in agreement with structure **88**. Unfortunately, the proton and carbon signals exhibit a far greater degree of complexity than one would first expect - all are complex multiplets. Such an observation could be explained by the existence of several conformational isomers of this 13-membered ring structure. However, NMR experiments performed at higher temperatures (47, 55, and 85°C) failed to produce any simplification of the proton or carbon spectra of the compound, suggesting that the conformational isomers of **88** are separated by energy barriers sufficient to preclude their interconversion even at 85°C. More reassuringly, high resolution mass spectrometry gave the correct elemental composition for the macrolide. On this basis it was concluded that this material was, in fact, **88**.

With the requisite macrocyclic diester in hand we turned to the execution of the Fries rearrangement. The use of aluminum chloride as catalyst at room temperature led to competing demethylation of the aryl ethers and gave **no** phenyl ketone products (that is, no products with an IR band of ca. 1680cm^{-1}). The substituent effects observed for the Fries rearrangement are essentially the same as those observed for electrophilic aromatic substitution.[46] Thus, **88**, with its methoxy and alkyl substituents, would be expected to be quite reactive toward electrophiles. For this reason the use of a milder catalyst, boron trifluoride etherate, was explored. To our surprise, however, this gave

no reaction other than gradual polymerization, while more traditional[47] ortho-Fries conditions (chlorobenzene, aluminum chloride, 120°C) gave, not unexpectedly, rapid polymerization. The extent to which polymerization occurs during this rearrangement may reflect, to some extent, the nature of competition between intermolecular[48] and intramolecular[49] mechanisms of the Fries rearrangement operating in the case of **88**.

Future efforts toward the desired Fries rearrangement might profit from an investigation of a wider variety of catalysts and solvents. It seems reasonable to suppose that the use of a more selective Lewis acid catalyst such as diethylaluminum chloride may be of some use in improving the above situation, because coordination of the oxygen atom of an aryl methyl ether is considerably more sterically demanding than coordination of a carbonyl oxygen. The photochemical variant of the Fries rearrangement may be useful, because it is known to proceed by a radical mechanism[50] rather than the ionic pathways usually written for the Lewis acid-catalyzed process. Thus, the photo-Fries rearrangement may be immune to the side reactions which rendered our attempts unsuccessful.

Another avenue for future investigation is that of a chiral entry into the bibenzyl system to afford enantiomerically pure **89**, which could lead to a stereo- and enantiospecific synthesis of byssochlamic acid. Since the ethyl epimers of **88** and **87** are interconvertible via the enol form, it should be possible to obtain the more stable diastereomer at each stage of the synthesis. Furthermore, the molecular modelling calculations discussed above indicate that the energy difference between these diastereomers is great enough to make this route to byssochlamic acid highly diastereoselective. Thus, further study of this synthetic problem appears to hold the promise of an eventual stereospecific synthesis of byssochlamic acid.

II-C. Experimental Section

All solvents for routine chromatography and reaction workup were reagent grade and were distilled through glass. Solvents for reactions were dried by distillation from an appropriate drying agent shortly before use. Tetrahydrofuran, ether, benzene, and toluene were distilled from potassium benzophenone ketyl under argon. Methylene chloride, triethylamine, diisopropylamine, pyridine, dimethyl sulfoxide, and dimethyl formamide were distilled from calcium hydride under argon. Starting materials and reagents were obtained from commercial suppliers unless otherwise noted.

Reaction flasks were oven-dried overnight at or above 165°C or flame dried and cooled in a desiccator over anhydrous calcium sulfate immediately prior to use. Syringes were oven-dried overnight and cooled in a desiccator as above. Removal of solvent was carried out under water aspirator pressure with a rotary evaporator and residual solvent was removed at the vacuum pump.

Flash chromatography was performed using E. Merck silica gel 60 (230-400 mesh ASTM) and an elution rate of approximately 2 inches per minute. Analytical thin layer chromatography was carried out with E. Merck precoated TLC plates (silica gel 60 F-254, 0.2mm layer thickness) cut to a size of 2.5 x 6.7 cm.

Nuclear magnetic resonance (NMR) spectra were obtained using either an IBM NR-80F or a Bruker AM-400 spectrometer. Chemical shifts are reported downfield from tetramethylsilane used as internal standard on the δ scale. ^{1}H NMR data are given in the following order: integral, multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; p, pentet; h, hextet; m, multiplet; b, broad), and coupling constants in Hertz. Infrared spectra (IR) were recorded on a Nicolet 5DXB FT instrument or a Perkin-Elmer 727B grating instrument. Ultraviolet spectra were determined on a Cary 210 UV/Vis. spectrophotometer and are reported with wavelength (λ) in nanometers. Routine mass spectra (MS) were measured on either a Varian MAT CH-7 or a Finnigan

4500 spectrometer using electron impact ionization at a potential of 70 eV unless otherwise noted. Exact mass measurements were performed with a Kratos MS-50 spectrometer. Melting points were determined with a Büchi melting point apparatus and are uncorrected. Elemental analyses were performed by Desert Analytics of Tucson, Arizona.

Molecular mechanics calculations utilized MODEL version KS 2.9 and MMX version 87 available from Serena Software, c/o Kosta Steliou, University of Montreal, and were run on a VAX 11-750.

2-Bromo-2-(bromomethyl) Succinic Acid (42)

To a solution of **41** (39.0g, 0.30mol) in acetic acid (50mL) at 105°C was added dropwise a solution of bromine (17mL, 0.31mol) in acetic acid (50mL) over about 2h. The resulting mixture was heated for a further 1.5h and evaporated to a syrup under reduced pressure. Carbon tetrachloride (100mL) was added and the mixture was again evaporated. Carbon tetrachloride (50mL) was added and the mixture was kept overnight at 0°C. The resulting solid was collected by filtration and washed with carbon tetrachloride. Evaporation of residual solvent at the pump afforded 57.2g(66%) of **42** as a white crystalline solid which was used without further purification: mp 164-165°C (lit.[22] 167-168°C).

2-Bromo-2-(bromomethyl) Succinic Anhydride (43)

A solution of **42** (57.0g, 0.197mol) in trifluoroacetic anhydride (60.0mL, 89.2g, 0.425mol) was heated at reflux for 30min.. The resulting mixture was evaporated to dryness to give 53.0g (99%) of **43** as a white crystalline solid: mp 58-59°C (lit.[22] 58-60°C); ^{1}H NMR (400MHz, $CDCl_3$) δ 4.23 (1H, d, J=10.8), 3.94 (1H, d, J=19.6), 3.90 (1H, d, J=10.8), 3.47 (1H, d, J=19.6); ^{13}C NMR (100MHz, $CDCl_3$) δ 167.4, 165.3, 50.0, 43.0, 32.7.

Bromocitraconic Anhydride (44)

To an ice-cooled mechanically stirred solution of **43** (53.0g, 0.195mol) in dry ether (250mL) was added over 1h a solution of triethylamine (19.7g, 27.3mL, 0.195mol) in dry ether (60mL). The resulting thick black suspension was stirred for a further 2h and slowly allowed to warm to room temperature. This mixture was filtered and concentrated to give an amber oil. Repeated flash chromatography on Florisil (1:1 ethyl acetate-hexanes) gave 0.30g (0.9%) of **44** as a colorless oil: IR (film) 3115, 1846, 1770, 1644, 1247cm^{-1}; ^{1}H NMR (400MHz, $CDCl_3$) δ 6.99 (1H, t, J=1.3), 4.28 (2H, d, J=1.3); ^{13}C NMR (100MHz, $CDCl_3$) δ 163.4, 162.6, 148.1, 131.7, 18.6.

Dimethyl Bromomethylfumarate (47)

To a stirred solution of **46** (15.8g, 0.10mol) in acetic acid (20mL) at 100°C was added dropwise a solution of bromine (5.4mL, 0.104mol) in acetic acid (20mL) over 1h. The mixture was heated a further 2h and evaporated under reduced pressure. Carbon tetrachloride (2 x 50mL) was added and evaporated to remove traces of acetic acid. The resulting amber liquid was distilled to afford 29.4g (93%) of dimethyl-1-bromomethyl-1-bromosuccinate as a colorless oil: bp 112-115°C @ 1.8mm/Hg. To a solution of this oil (5.0g, 15.7mmol) in tetrahydrofuran (30mL) was added diisopropylethylamine (2.03g, 2.74mL, 15.7mmol) and the mixture was heated at reflux for 24h. The resulting amber solution and copious white precipitate were diluted with ether (100mL) and washed with water (3 x 20mL). Drying over sodium sulfate, filtration, and evaporation gave 3.69g (99%) of **47** as a brown oil suitable for further transformation. Further purification could be effected by distillation of this oil to give a colourless oil: bp 103-105°C @ 1.9mm/Hg (lit.[27] 86-89°C @ 2mm/Hg); IR (film) 2955, 1719, 1283cm^{-1}; ^{1}H NMR (400MHz, $CDCl_3$) δ 6.84 (1H, s), 4.73 (2H, s),

3.88 (3H, s), 3.83 (3H, s); ^{13}C NMR (100MHz, $CDCl_3$) δ 165.3, 165.1, 142.8, 128.3, 52.7, 51.9, 22.0; MS *m/z* 239, 237, 207, 205, 179, 177, 157.

(E,Z)-Tetramethyl 1,5-Hexadiene-1,2,5,6-tetracarboxylate (48) and (E,E)-Tetramethyl 1,5-Hexadiene-1,2,5,6-tetracarboxylate (49)

To a solution of **47** (1.87g, 7.90mmol) in tetrahydrofuran (40mL) at room temperature was added nickel tetracarbonyl (4.10mL, 5.38g, 31.6mmol). The reaction mixture was stirred for 3h at room temperature by which time gas evolution had ceased and the reaction mixture consisted of a red solution with a white precipitate. This mixture was evaporated to dryness and extracted with ether (3 x 25mL). The combined extracts were washed with 0.1N hydrochloric acid (2 x 20mL) and water (2 x 20mL). Evaporation gave 1.22g of colorless oil which was subjected to flash chromatography on silica (25% ethyl acetate-hexanes) to give 363mg of **49** followed by 670mg of **48** (83% combined yield); **48**: IR (film) 2956, 1730, 1719, 1653, 1648, 1265cm^{-1}; ^1H NMR (400MHz, $CDCl_3$) δ 6.83 (1H, s), 5.92 (1H, s), 3.85 (3H, s), 3.82 (3H, s), 3.78 (3H, s), 3.74 (3H, s), 2.99 (2H, t, J=8.3), 2.53 (2H, t, J=8.3); ^{13}C NMR (100MHz, $CDCl_3$) δ 168.5, 166.5, 165.5, 165.3, 148.1, 145.4, 127.8, 120.6, 52.6, 52.2, 51.8, 51.7, 33.1, 25.8; UV (methanol) 233 (ε 10980); **49**: IR (film) 2955, 1730, 1653, 1281cm^{-1}; ^1H NMR (400MHz, $CDCl_3$) δ 6.77 (2H, s), 3.83 (6H, s), 3.72 (6H, s), 3.09 (4H, s); ^{13}C NMR (100MHz, $CDCl_3$) δ 166.8, 165.8, 145.7, 127.5, 52.5, 51.7, 26.2.

(Z,Z)-Tetramethyl 1,5-Hexadiene-1,2,5,6-tetracarboxylate (50)

A solution of **48** (157mg, 0.50mmol) in benzene (100mL) was irradiated with a 450W Hanovia medium pressure mercury lamp through Pyrex for 4h. Evaporation of the resulting colorless solution gave 214mg of colorless oil. Flash chromatography of this oil on silica (1:1 ethyl acetate-hexanes) gave 152mg (97%) of **50** as a colorless oil:

IR (film) 2956, 1729, 1653, 1280, 1272, 1260cm^{-1}; ^{1}H NMR (400MHz, $CDCl_3$) δ 5.89 (2H, s), 3.84 (6H, s), 3.73 (6H, s), 2.57 (4H, s); ^{13}C NMR (100MHz, $CDCl_3$) δ 168.5, 165.2, 147.0, 121.5, 52.5, 52.0, 31.7; MS *m/z* 314(M+), 283, 282, 255, 250, 223, 222; Calcd for $C_{14}H_{18}O_8$: 314.1001. Found: 314.1001.

Di-t-butyl 2-(Bromomethyl)-2-bromosuccinate (51)

A mixture of **42** (12.0g, 41.4mmol), isobutylene (50mL), and concentrated sulfuric acid (1mL) in a thick-walled pressure bottle was shaken on a Parr apparatus for 8h. At that time the original suspension had become an amber solution. This solution was chilled in an ice-acetone bath to reduce the pressure and the stopper was removed. After dilution with ether (100mL), the solution was washed with 1N sodium hydroxide (20mL), saturated aqueous sodium bicarbonate (20mL), water (2 x 20mL), and brine (20mL). The ethereal solution so obtained was dried over sodium sulfate, filtered, and evaporated to give 19.0g of maroon oil. This oil was filtered through silica (elution with 1:1 ethyl acetate-hexanes) to afford 15.0g (90%) of **51** as an amber oil. For the purposes of characterization a pure sample of **51** could be obtained by recrystallization from ethanol-water: mp 47-47.5°C; IR (film) 2981, 1742, 1730, 1167cm^{-1}; ^{1}H NMR (400MHz, $CDCl_3$) δ 4.28 (1H, d, J=10.4), 4.23 (1H, d, J=10.4), 3.27 (2H, s), 1.51 (9H, s), 1.47 (9H, s); ^{13}C NMR (100MHz, $CDCl_3$) δ 168.1, 166.3, 83.4, 81.7, 57.2, 41.9, 37.1, 27.9, 27.5; MS *m/z* 338, 331, 329, 293, 291, 289, 223, 221; Anal. Calcd for $C_{13}H_{22}Br_2O_4$: C, 38.83; H, 5.51; Br, 39.74. Found: C, 39.01; H, 5.51; Br, 39.46.

Di-t-butyl Bromomethylfumarate (52)

A solution of 1,8-diazabicyclo[5.4.0]undec-7-ene (0.57mL, 0.58g, 3.8mmol) in tetrahydrofuran (5mL) was added dropwise to a solution a **51** (1.4g, 3.5mmol) in tetrahydrofuran (5mL), stirred at -10°C. The reaction was allowed to warm to room

temperature and was was stirred for 1h at this temperature. The resulting amber suspension was diluted with ether (50mL) and washed with water (2 x 20mL). Drying over sodium sulfate, filtration, and evaporation gave 1.05g of brown oil. Flash chromatography of this material on silica (10% ethyl acetate-hexanes) gave 0.77g (69%) of **52** as a colorless oil: IR (film) 2980, 1718, 1716, 1292, 1142cm^{-1}; ^{1}H NMR (400MHz, $CDCl_3$) δ 6.64 (1H, s), 4.64 (2H, s), 1.54 (9H, s), 1.53 (9H, s); ^{13}C NMR (100MHz, $CDCl_3$) δ 164.2, 164.0, 142.6, 130.0, 82.8, 28.1, 27.9, 23.1.

(E,Z)-Tetra-t-butyl 1,5-Hexadiene-1,2,5,6-tetracarboxylate (53)

Nickel tetracarbonyl (0.54g, 0.40mL, 3.2mmol) was added to a solution of **52** (0.20g, 0.63mmol) in tetrahydrofuran (5mL). The reaction mixture was stirred at room temperature until gas evolution had ceased (ca. 2h) at which time it was evaporated to dryness. Trituration of the resulting solid with ether (3 x 25mL) and evaporation of the extract so obtained gave 140mg of a colorless oil. Flash chromatography of this oil on silica (10% ethyl acetate-hexanes) gave 130mg (86%) of **53** as a colorless oil: IR (film) 2979, 1719, 1650, 1369, 1277, 1155cm^{-1}; ^{1}H NMR (400MHz, $CDCl_3$) δ 6.26 (1H, s), 5.75 (1H, s), 2.88 (2H, m), 2.43 (2H, m), 1.54 (9H, s), 1.51 (9H, s), 1.50 (9H, s), 1.47 (9H, s); ^{13}C NMR (100MHz, $CDCl_3$) δ 167.6, 165.7, 164.9, 164.3, 148.5, 146.0, 128.8, 121.1, 82.0, 81.9, 81.4, 80.7, 33.4, 28.1, 28.0(2), 26.0; MS *m/z* 455, 447, 409, 361, 360, 353, 350, 343, 338, 315, 312, 307, 291, 249, 207, 202, 184, 180, 141, 103.

3-(Bromomethyl)-4-hydroxy-2-butenoic Acid Lactone (59)

A solution of senecioic acid (**57**) (25.0g, 0.25mol) and N-bromosuccinimide (93.5g, 0.53mol) in carbon tetrachloride (500mL) was heated at reflux and benzoyl peroxide (0.50g) was added. After 2h at reflux a second portion of benzoyl peroxide (0.25g) was added and heating was continued for an additional 2h. The resulting white

suspension was filtered and evaporated to give 107g of **58** as a golden oil. To the crude **58** was added dropwise 5% aqueous sodium hydroxide (200mL, 0.25mol) over 1h, and the milky mixture was stirred at room temperature. This mixture was then extracted with methylene chloride (3 x 50mL). The combined extracts were washed with saturated aqueous sodium bicarbonate (30mL) and water (2 x 25mL). After drying over magnesium sulfate the organic solution was filtered and evaporated to give an amber oil. Distillation of this oil afforded 20.8g (47%) of **59** as a straw colored oil: bp 120-125°C @ 0.4mm/Hg (lit.[32] 118-121 @ 0.6mm/Hg). Further purification could be effected by flash chromatography on silica (1:1 ethyl acetate-hexanes) to give a colorless oil: IR (film) 1785, 1744, 1642, 1322, 1147, 1124, 1032cm^{-1}; ^{1}H NMR (400MHz, $CDCl_3$) δ 6.16 (1H, s), 4.98 (2H, s), 4.33 (2H, s); ^{13}C NMR (100MHz, $CDCl_3$) δ 172.9, 164.3, 118.4, 71.5, 22.2; MS *m/z* 178, 176, 149, 147, 96.

3-Phenylthio-4-hydroxy-2-butenoic Acid Lactone (60)

Sodium hydride (60% in oil, 216mg, 5.40mmol) was washed free of oil with dry pentane (2 x 2mL) and suspended in tetrahydrofuran (5mL). Thiophenol (0.50mL, 540mg, 4.87mmol) was added and the mixture was stirred until gas evolution ceased (ca. 15min.). A solution of **59** (850mg, 4.80mmol) in tetrahydrofuran (6mL) was then added at 0°C. The mixture was allowed to warm to room temperature and was stirred for 2h. The resultant green suspension was diluted with ether (40mL), filtered, evaporated, and subjected directly to flash chromatography on silica (25% ethyl acetate-hexanes) to afford 779mg (79%) of **60** as a colorless oil which solidified on standing: IR (film) 1780, 1747, 1440, 1031, 738cm^{-1}; ^{1}H NMR (80MHz, $CDCl_3$) δ 7.35-7.26 (5H, m), 5.79 (1H, s), 4.82 (2H, s), 3.84 (2H, s); ^{13}C NMR (100MHz, $CDCl_3$) δ 173.2, 165.5, 133.8, 131.0, 129.4, 127.9, 117.7, 71.9, 31.8.

3-Phenylsulfoxymethyl-4-hydroxy-2-butenoic Acid Lactone (61)

m-Chloroperbenzoic acid (85% tech., 620mg, 3.06mmol) was added to an ice-cooled, stirred solution of **60** (573mg, 2.78mmol) in methylene chloride (25mL). The suspension was warmed to room temperature and stirred for 1h. After quenching with 0.5M sodium thiosulfate (50mL), the layers were separated and the aqueous phase was extracted with methylene chloride (2 x 25mL). The combined organics were dried over magnesium sulfate, filtered and evaporated to give 750mg of a solid. Flash chromatography of this material on silica (ethyl acetate) gave 531mg (86%) of **61** as a white crystalline solid: mp 106.5-107°C(methylene chloride/hexanes); IR (Nujol) 1784, 1628, 1031cm^{-1}; ^{1}H NMR (400MHz, $CDCl_3$) δ 7.56 (5H, s), 5.72 (1H, br s), 4.84 (1H, dd, J=18.3, 1.5), 4.48 (1H, br d, J=18.3), 4.06 (1H, d, J=13.4), 3.74 (1H, d, J=13.4); ^{13}C NMR (100MHz, $CDCl_3$) δ 172.4, 156.8, 141.4, 132.0, 129.6, 123.9, 120.8, 73.7, 54.5; MS *m/z* 222, 125, 109, 97, 77; Anal. Calcd for $C_{11}H_{10}O_3S$: C, 59.44; H, 4.54; S, 14.43. Found: C, 59.38; H, 4.49; S, 14.44.

3-(O,O-Diethylphosphonomethyl)-4-hydroxy-2-butenoic Acid Lactone (62)

Freshly distilled triethyl phosphite (4.1mL, 3.98g, 24.0mmol) was heated to 80°C and **59** (3.54g, 20.0mmol) was added dropwise over 1h, while maintaining the internal temperature below 90°C. The resulting orange solution was stirred for 2h at 90-95°C, during which time the ethyl bromide byproduct was distilled from the mixture. Any excess triethyl phosphite was removed under reduced pressure at 95°C to give 5.25g (86%) of **62** as an amber oil: IR (film) 2985, 1751, 1642, 1051, 1032, 970cm^{-1}; ^{1}H NMR (400MHz, $CDCl_3$) δ 6.06 (1H, m), 4.90 (2H, m), 4.16 (4H, m), 3.06 (2H, d, 22.9), 1.35 (6H, br t, J=7.1); ^{13}C NMR (100MHz, $CDCl_3$) δ 172.9, 160.4 (d, J=10.0), 118.3 (d, J=10.0), 72.6 (d, J=4.2), 61.9 (d, J=6.7), 26.3 (d, 38.6), 15.2 (d, J=5.9).

3-Phenylsulfonylmethyl-4-hydroxy-2-butenoic Acid Lactone (63)

Sodium phenylsulfinate (282mg, 1.72mmol) was added to a stirred solution of **59** (276mg, 1.56mmol) in dry dimethylformamide (2mL) and the deep red mixture was stirred 3h at room temperature. The resulting mixture was diluted with ether (20mL) and quenched with 1M ammonium acetate (15mL). The layers were separated and the aqueous fraction was extracted with ethyl acetate (3 x 25mL). The combined organics were dried over magnesium sulfate, filtered, and evaporated to give 440mg of a solid. Flash chromatography of this solid on silica (ethyl acetate) gave 304mg (82%) of **63** as a white crystalline solid: mp 128-128.5°C (acetone-hexanes; lit.[35] 125°C); IR (Nujol) 1750, 1313, 1145cm^{-1}; ^{1}H NMR (400MHz, $CDCl_3$) δ 7.9-7.6 (5H, m), 5.89 (1H, s), 4.94 (2H, s), 4.22 (2H, s); ^{13}C NMR (100MHz, $CDCl_3$) δ 174.7, 158.8, 139.4, 135.7, 130.7, 129.4, 122.8, 74.5; MS *m/z* 238, 141, 125, 97, 77.

3-Nitratomethyl-4-hydroxy-2-butenoic Acid Lactone (64)

Silver nitrate (4.7g, 28mmol) was added to a solution of **59** (500mg, 2.82mmol) in acetonitrile (10mL) and the milky suspension was stirred for 3h at room temperature. The resulting mixture was diluted with water (25mL) and extracted with ether (3 x 25mL). The combined ethereal extracts were dried over sodium sulfate, filtered, and evaporated to give 400mg of an amber oil. Flash chromatography of this oil on silica (1:1 ethyl acetate-hexanes) gave 280mg (62%) of **64** as a colorless oil: IR (film) 1786, 1751, 1655, 1282, 856, 754cm^{-1}; ^{1}H NMR (400MHz, $CDCl_3$) δ 6.17 (1H, q, J=1.8), 5.38 (2H, m), 4.91 (2H, d, J=2.0); ^{13}C NMR (100MHz, $CDCl_3$) δ 172.5, 160.3, 118.9, 70.8, 66.7; MS *m/z* 337(M+), 159; Calcd for $C_5H_5NO_5$: 159.0168. Found: 159.0168.

3-(1-Phenylsulfonylbutyl)-4-hydroxy-2-butenoic Acid Lactone (66)

Sodium hydride (60% in oil, 18mg, 0.45mmol) was washed free of oil with dry pentane (2 x 1mL) and suspended in dry dimethylformamide (2mL). To this suspension was added **63** (100mg, 0.42mmol) and the mixture was stirred at room temperature until gas evolution had ceased (15min.) to give an orange solution. n-Propyl bromide (45μL, 62mg, 0.50mmol) was added and the mixture was stirred overnight at room temperature. Ether (25mL), followed by water (10mL), was added and the layers were separated. The aqueous phase was extracted with ether (2 x 20mL) and the combined organics were dried over sodium sulfate, filtered, and evaporated to give 75mg (67%) of **66** as an amber oil: IR (film) 2966, 1753, 1634, 1310, 1148cm^{-1}; ^{1}H NMR (400MHz, $CDCl_3$) δ 7.9-7.5 (5H, m), 5.81 (1H, t, J=1.6), 4.94 (1H, dd, J=18.2, 1.8), 4.82 (1H, dd, J=18.2, 1.8), 4.01 (1H, dd, J=11.6, 3.5), 2.3-2.1 (1H, m), 1.9-1.7 (1H, m), 1.5-1.3 (2H, m), 0.94 (3H, t, J=7.3); ^{13}C NMR (100MHz, $CDCl_3$) δ 171.9, 160.2, 136.1, 134..7, 129.5, 129.0, 122.1, 72.3, 65.4, 29.2, 18.1, 13.6.

3-(1-Phenylsulfonylpropyl)-4-hydroxy-2-butenoic Acid Lactone (67) and 3-(1-Phenylsulfonyl-1-ethylpropyl)-4-hydroxy-2-butenoic Acid Lactone (68)

A 1.5M solution of n-butyllithium in hexanes (0.67mL, 1.01mmol) was added to a stirred solution of diisopropylamine (145μL, 105mg, 1.03mmol) in tetrahydrofuran (2mL) at -78°C. After 15min. at this temperature a solution of **63** (102mg, 0.46mmol) in tetrahydrofuran (3mL) was added. The orange mixture was warmed to room temperature for 15min. and cooled to -78°C, and ethyl iodide (111μL, 216mg, 1.38mmol) was added. Stirring was continued for 1h at -78°C. The orange mixture was then allowed to warm to room temperature over about 3h. After dilution with ether (15mL) the reaction was quenched by addition of saturated aqueous

ammonium chloride (10mL). The layers were separated and the aqueous phase was extracted with ether (3 x 20mL). The combined organics were dried over sodium sulfate, filtered, and evaporated to afford 118mg of an amber oil. Flash chromatography of this oil on silica (1:1 ethyl acetate-hexanes) gave first 45mg (33%) of **68** as a white crystalline solid followed by 42mg (35%) of **67** as a colorless oil; **67**: IR (film) 1752, 1309, 1148cm^{-1}; ^{1}H NMR (400MHz, $CDCl_3$) δ 7.9-7.6 (5H, m), 5.85 (1H, t, J=2.0), 4.95 (1H, dd, J=18.0, 2.0), 4.84 (1H, dd, J=18.0, 2.0), 3.94 (1H, dd, J=11.4, 3.6), 2.32-2.25 (1H, m), 1.90-1.75 (1H, m), 0.99 (3H, t, J=7.4); **68**: IR (film) 2977, 1755, 1742, 1310, 1151cm^{-1}; ^{1}H NMR (400MHz, $CDCl_3$) δ 7.78-7.53 (5H, m), 5.56 (1H, s), 5.02 (2H, s), 2.27 (2H, dq, J=7.5, 7.5), 1.92 (2H, dq, J=7.5, 7.5), 1.08 (6H, t, J=7.5); ^{13}C NMR (100MHz, $CDCl_3$) δ 172.0, 165.3, 134.6, 130.0, 129.0, 122.2, 121.3, 85.2, 72.3, 22.3, 8.0; MS *m/z* 294, 153; Calcd for $C_{15}H_{18}O_4S$: 294.09264. Found: 294.09262.

2,5-Dimethoxybenzyl Bromide (77)

To a rapidly stirred suspension of N-bromosuccinimide (4.70g, 26.2mmol) in methylene chloride (100mL) at 0°C was added dimethyl sulfide (2.10mL, 1.77g, 28.5mmol) over about 2min. To this yellow slurry was added a solution of **76** (4.0g, 23.8mmol) in methylene chloride (10mL). The resulting mixture was allowed to warm to room temperature and stirred for 3h. The reaction mixture was then washed with water (2 x 30mL), dried over sodium sulfate, filtered and evaporated to give 5.58g of a yellow crystalline solid. Flash chromatography of this solid on silica (25% ethyl acetate-hexanes) gave 4.81g (91%) of **77** as a white crystalline solid: IR (film) 2964, 1460, 1422, 1209, 1023, 811cm^{-1}; ^{1}H NMR (400MHz, $CDCl_3$) δ 6.9-6.7 (3H, m), 4.55 (2H, s), 3.82 (3H, s), 3.75 (3H, s); ^{13}C NMR (100MHz, $CDCl_3$) δ 153.8, 152.0, 127.2, 116.6, 115.2, 112.4, 56.1, 55.7, 28.5.

2,2',5,5'-Tetramethoxybibenzyl (69)

A 0.1M solution of samarium diiodide in tetrahydrofuran was prepared by dropwise addition of a solution of 1,2-diiodoethane (5.07g,18mmol) in tetrahydrofuran (150mL) to a stirred suspension of powdered samarium metal (5.4g, 36 mmol) in tetrahydrofuran (30mL) until a blue color formed. At this time the remaining diiodoethane solution (ca. 100mL) was added rapidly. The resulting mixture was stirred overnight at room temperature. The dark blue samarium diiodide solution was then added via cannula to a stirred solution of **77** (1.0g, 4.5mmol) in tetraydrofuran (10mL) to produce a persistent blue color (ca. 50mL, 5.0mmol of samarium diiodide). The excess samarium diiodide in this mixture was quenched by the addition of 1.0M aqueous ammonium acetate (20mL) and the product was extracted with ether (3 x 25mL). The combined extracts were dried over sodium sulfate, filtered, and evaporated to give 0.68g (100%) of **69** as a colorless oil, which solidified on standing: IR (film) 2946, 1506, 1223, 1047cm^{-1}; ^{1}H NMR (400MHz, $CDCl_3$) δ 6.78-6.67 (6H, m), 3.77 (6H, s), 3.73 (6H, s), 2.85 (4H, s); ^{13}C NMR (100MHz, $CDCl_3$) δ 153.8, 152.2, 132.2, 116.4, 111.6, 111.3, 56.0, 55.6, 30.4; MS *m/z* 302, 151, 121; Calcd for $C_{18}H_{22}O_4$: 302.15186. Found: 302.15182.

2,2'-(1,2-Ethanediyl) bis-[2,5-Cyclohexadiene-1,4-dione] (70)

To a solution of **69** (275mg, 0.91mmol) in acetonitrile (10mL) was added a solution of ceric ammonium sulfate (4.00g, 7.28mmol) in water (15mL). After 15min. the golden suspension was extracted with chloroform (5 x 15mL). The combined extracts were evaporated and the residue was subjected to flash chromatography on (Mallinckrodt) Silicar CC-4 (methylene chloride) to give 38mg (17%) of **70** as an amorphous yellow solid: IR (film) 1663, 1603, 1291, 912cm^{-1}; ^{1}H NMR (400MHz, $CDCl_3$) δ 6.78 (2H, d, J=10.0), 6.74 (2H, dd, J=2.1, 10.0), 6.58 (2H, d, J=2.1), 2.67 (4H, s); ^{13}C NMR (100MHz, $CDCl_3$) δ 187.3, 187..1, 147.5, 136.8, 136.5,

133.1, 27.8; MS *m/z* 242, 165, 84; Calcd for $C_{14}H_{10}O_4$: 242.0579. Found: 242.0583.

2',5'-Dimethoxybutyrophenone (79)

A mixture of **78** (11.0g, 80.0mmol), butyric acid (8.8g, 9.2mL, 100mmol), and polyphosphoric acid (17g, excess) was stirred at 115°C for 3h. The resulting brown mixture was quenched with water (100mL) and extracted with methylene chloride (4 x 50mL). The combined extracts were washed with 1M sodium hydroxide (2 x 25mL) and 3M hydrochloric acid (25mL), and dried over sodium sulfate. The resulting solution was filtered through a short plug of silica (methylene chloride elution) and evaporated to give 12.3g of a brown oil containing a large amount of **78**. Fractional distillation gave 3.24g (19%, 27% based on recovered **78**) of **79** as a golden oil: bp 123-127°C @ 0.08mm/Hg; IR (film) 2962, 1675, 1496, 1223, 1049cm^{-1}; ^{1}H NMR (400MHz, $CDCl_3$) δ 7.22 (1H, d, J=3.3), 6.98 (1H, dd, J=8.9, 3.3), 6.88 (1H, d, J=8.9), 3.84 (3H, s), 3.77 (3H, s), 2.95 (2H, t, J=7.3), 1.70 (2H, h, J=7.4), 0.96 (3H, t, J=7.5); ^{13}C NMR (100MHz, $CDCl_3$) δ 202.4, 153.3, 152.7, 128.8, 119.2, 113.8, 112.9, 55.9, 55.6, 45.5, 17.7, 13.8; MS *m/z* 208, 16.

1,2-bis(2,5-Dimethoxyphenyl)-2-pentanol (80)

To a stirred solution of **77** (223mg, 1.0mmol) and **79** (139mg, 0.67mmol) in tetrahydrofuran (5mL) was added a 0.1M solution of samarium diiodide in tetrahydrofuran (18mL, 1.8mmol, see above preparation of **69**) and the mixture was stirred for 0.5h at room temperature. Hydrochloric acid (0.1M, 20mL) was added and the resulting brown mixture was extracted with ether (3 x 25mL). The combined extracts were dried over magnesium sulfate, filtered, and evaporated to give 317mg of a yellow oil. Flash chromatography of this oil gave 209mg (87%) of **80** as a colorless oil: IR (film) 3400, 2957, 1500, 1466, 1221, 1050, 734cm^{-1}; ^{1}H NMR (400MHz,

$CDCl_3$) δ 7.0-6.4 (6H, m), 3.84 (3H, s), 3.75 (3H, s), 3.69 (3H, s), 3.61 (3H, s), 3.30 (2H, AB, J=18.0), 2.19 (1H, dt, J=12.0, 4.4), 1.72 (1H, dt, J=4.5, 12.0), 1.42-1.35 (1H, m), 1.05-0.99 (1H, m), 0.83 (3H, t, J=7.3); ^{13}C NMR (100MHz, $CDCl_3$) δ 153.5, 153.4, 151.8, 150.5, 135.6, 127.7, 118.4, 114.8, 112.2, 111.7 (2), 111.2, 78.0, 56.0, 55.8, 55.7, 55.6, 42.3, 41.5, 17.3, 14.6; MS *m/z* 360, 209; Calcd for $C_{21}H_{28}O_5$: 360.19374. Found: 360.19375.

1,2-bis(2,5-Dimethoxyphenyl)pentane (81)

A mixture of **80** (470mg, 1.30mmol), ethanol (30mL), perchloric acid (1.5mL), and 10% palladium on charcoal (200mg) was stirred under an atmosphere of hydrogen for 72h. The acid was neutralized with 1M sodium hydroxide and the product was extracted into ether (4 x 50mL). The combined extracts were dried over magnesium sulfate, filtered, and evaporated to yield 426mg of an amber oil. Flash chromatography of this oil on silica (25% ethyl acetate-hexanes) gave 347mg (77%) of **81** as a colorless oil: IR (film) 2937, 1498, 1464, 1223, 1050cm^{-1}; ^1H NMR (400MHz, $CDCl_3$) δ 6.75-6.52 (6H, m), 3.75 (3H, m), 3.74 (3H, m), 3.67 (3H, m), 3.63 (3H, m), 3.43 (1H, br p, J=7.4), 2.91 (1H, dd, J=13.4, 7.1), 2.73 (1H, dd, J=13.4, 7.7), 1.58 (2H, m), 1.18 (2H, m), 0.81 (3H, t, J=7.3); ^{13}C NMR (100MHz, $CDCl_3$) δ 153.7, 153.2, 153.1, 152.2, 135.8, 130.9, 116.6, 114.3, 112.0, 111.2, 110.5, 56.4, 56.1, 55.8, 55.7, 38.0, 37.0, 36.4, 20.7, 14.2; MS *m/z* 344, 193, 151, 121; Calcd for $C_{21}H_{28}O_4$: 344.19884. Found: 344.19907.

1,2-bis(2,5-Dihydroxyphenyl)pentane (82)

To a stirred solution of **81** (105mg, 0.30mmol) in methylene chloride (3mL) at -78°C was added a 1.0M solution of boron tribromide in hexanes (1.52mL, 1.52mmol) and the mixture was allowed to warm to room temperature overnight. Water (5mL) was then added and the product was extracted with ethyl acetate (3 x 15mL).

The combined extracts were dried over sodium sulfate, filtered, and evaporated to give 125mg of an amber oil. Flash chromatography of this oil on silica (1:1 ethyl acetate-hexanes) gave 80mg (91%) of **82** as a colorless oil: IR (film) 3300, 2958, 1505, 1456, 1198cm^{-1}; ^{1}H NMR (400MHz, $CDCl_3$) δ 6.64-6.43 (6H, m), 3.29-3.25 (1H, m), 2.76 (1H, dd, J=13.5, 6.1), 2.69 (1H, dd, J=13.5, 8.4), 1.67-1.58 (2H, m), 1.25-1.09 (2H, m), 0,81 (3H, t, J=7.4); ^{13}C NMR (100MHz, $CDCl_3$) δ 151.1, 150.8, 149.4, 149.3, 134.1, 129.9, 118.5, 117.0, 116.7, 115.3, 114.2, 113.9, 39.7, 37.8, 36.9, 21.6, 14.5; MS *m/z* 288, 193, 151, 123; Calcd for $C_{17}H_{20}O_4$: 288.1362. Found: 288.1363.

2,2'-(1-Propyl-1,2-Ethanediyl) bis-[2,5-Cyclohexadiene-1,4-dione] (83)

To a solution of **82** (75mg, 0.26mmol) in acetonitrile (3mL) was added a solution of ceric ammonium nitrate (0.60g, 1.1mmol) in water (2mL) at room temperature. After 10 min. the yellow mixture was extracted with chloroform (3 x 15mL). The combined extracts were dried over sodium sulfate, filtered, and evaporated to give 67mg (90%) of **83** as a yellow oil: IR (film) 2960, 1655, 1600, 1293, 910cm^{-1}; ^{1}H NMR (400MHz, $CDCl_3$) δ 6.83-6.69 (4H, m), 6.46 (2H, dd, J=18.0, 2.1), 3.10 (1H, br p, J=7.2), 2.83 (1H, dd, J=14.0, 6.3), 2.52 (1H, dd, J=14.0, 8.8), 1.59 (2H, m), 1.27 (2H, m), 0.90 (3H, t, J=7.3); ^{13}C NMR (100MHz, $CDCl_3$) δ 187.4, 187.2, 187.1, 187.0, 150.9, 146.7, 137.0, 136.7, 136.3, 136.0, 133.5, 132.5, 37.3, 36.0, 34.2, 20.4, 13.8; UV (acetonitrile) 315 (ε 870), 246 (ε 27000); MS *m/z* 284, 255, 162, 123; Calcd for $C_{17}H_{16}O_4$: 284.10490. Found: 284.10500.

1,2-bis(2,5-Dimethoxy-4-acetophenyl)pentane (84)

To a rapidly stirred suspension of aluminum chloride (650mg, 4.90mmol) in methylene chloride (10mL) was added acetyl chloride (320mg, 290μL, 4.08mmol). After 5min. this mixture was cooled to 0°C and a solution of **81** (560mg, 1.63mmol)

in methylene chloride (5mL) was added. After 1h the reaction was quenched with 10% aqueous sodium hydroxide (10mL) and extracted with methylene chloride (3 x 20mL). The combined extracts were dried over magnesium sulfate, filtered, and evaporated to give 683mg of a colorless oil. Flash chromatography of this oil on silica (1:1 ethyl acetate-hexanes) afforded 507mg (73%) of **84** as white plates: mp 94.5-95.5°C (hexanes); IR (film) 2957, 1670, 1664, 1497, 1229, 1216, 1044, 1039cm^{-1}; ^{1}H NMR (400MHz, $CDCl_3$) δ 7.27 (1H, s), 7.24 (1H, s), 6.70 (1H, s), 6.48 (1H, s), 3.82 (3H, s), 3.79 (3H, s), 3.70 (3H, s), 3.67 (3H, s), 3.01 (1H, dd, J=13.6, 5.9), 2.87 (1H, dd, J=13.6, 9.0), 2.59 (3H, s), 2.57 (3H, s), 1.66 (2H, q, J=7.6), 1.24 (2H, m), 0.87 (3H, t, J=7.3); ^{13}C NMR (100MHz, $CDCl_3$) δ 198.8, 198.7, 153.8, 153.3, 151.7, 151.6, 140.6, 136.0, 125.6, 125.5, 114.6, 112.2, 111.8, 111.1, 56.1, 56.0, 55.9, 38.5, 37.2, 35.7, 32.0, 20.7, 14.1; MS *m/z* 428, 235, 193; Calcd for $C_{25}H_{32}O_6$: 428.21996. Found: 428.21979. Anal. Calcd for $C_{25}H_{32}O_6$: C, 70.07; H, 7.53. Found: C, 70.09; H, 7.50.

1,2-bis(2,5-Dimethoxy-4-ethylphenyl)pentane (85)

A stirred solution of **84** (36mg, 0.086mmol), potassium hydroxide (0.96g, 17.2mmol), and hydrazine monohydrate (1.5mL, 31mmol) in diethylene glycol (10mL) was heated at 140°C for 1h and then at 205°C for 2h. The resulting mixture was cooled to room temperature and diluted with water (10mL). Brine (20mL) was added and the product was extracted with ether (3 x 15mL). Drying over magnesium sulfate, filtration, and evaporation gave 106mg of a colorless oil. Flash chromatography of this oil on silica (10→25% ethyl acetate-hexanes) gave 19.3mg (57%) of **85** as a colorless oil: IR (film) 2958, 2933, 1506, 1465, 1405, 1208, 1048cm^{-1}; ^{1}H NMR (400MHz, $CDCl_3$) δ 6.65-6.36 (4H, m), 3.75 (3H, s), 3.74 (3H, s), 3.60 (3H, s), 3.59 (3H, s), 3.37 (1H, br p, J=7.0), 2.92 (1H, dd, J=13.5, 6.5), 2.72 (1H, dd, J=13.5, 6.5), 2.60-2.52 (4H, m), 1.61 (2H, m), 1.12-1.24 (8H, m), 0.83 (3H, t, J=7.3); ^{13}C NMR

(100MHz, $CDCl_3$) δ 1551.8, 151.7, 151.5, 150.7, 132.4, 130.4, 130.3, 127.6, 113.9, 113.1, 112.1, 110.9, 56.7, 56.2, 56.1, 56.0, 38.1, 37.2, 36.0, 23.2, 23.1, 20.7, 14.5, 14.2; MS *m/z* 400, 221, 179; Calcd for $C_{25}H_{36}O_4$: 400.26148. Found: 400.26159.

Bisquinone 86

To a stirred solution of **85** (110mg, 0.28mmol) in methylene chloride (10mL) at -78°C was added a 1.0M solution of boron tribromide in hexanes (1.4mL, 1.4mmol). The mixture was allowed to warm to room temperature and stirring was continued for 18h. Water (10mL) was added and the product was extracted with ethyl acetate (3 x 20mL). Drying over sodium sulfate, filtration, and evaporation gave 170mg of a colorless semi-solid. Flash chromatography on silica (1:1 ethyl acetate-hexanes) gave 93mg of the gummy solid hydroquinone. To a stirred solution of this material (69mg, 0.20mmol) in acetonitrile (5mL) at room temperature was added a solution of ceric ammonium nitrate (0.44g, 0.80mmol) in water (5mL). After 10min. the resultant orange mixture was extracted, dried over sodium sulfate, filtered, and evaporated to afford 67mg (99%) of **86** as yellow needles: mp 119.5-120°C (ethanol-water); IR (film) 2964, 1653, 1648cm^{-1}; ^1H NMR (400MHz, $CDCl_3$) δ 6.52-6.40 (4H, m), 3.06 (1H, br p, J=6.2), 2.78 (1Hm, ddd, J=14.1, 5.8, 1.2), 2.49 (1H, dd, J=14.0, 8.9), 2.47-2.39 (4H, m), 1.55 (2H, m), 1.25 (2H, m), 1.12 (6H, m), 0.88(3H, t, J=7.3); ^{13}C NMR (100MHz, $CDCl_3$) δ 187.7, 187.6, 187.5, 150.7, 150.3, 146.5, 133.8, 132.8, 132.1, 131.8, 37.2, 36.3, 33..8, 21.8, 21.7, 20.5, 13.9, 11.5; UV (acetonitile) 252 (ε 26,900); MS *m/z* 340, 311, 297, 191, 151. Anal. Calcd for $C_{21}H_{24}O_4$: C, 74.09; H, 7.11. Found: C, 73.91; H, 7.06.

1,2-bis(2-Hydroxy-5-t-butyldiphenylsiloxyphenyl)pentane (91)

To a stirred solution of **82** (25mg, 0.087mmol) and imidazole (30mg, 0.43mmol) in dry dimethylformamide (1mL) was added t-butyldiphenylsilyl chloride (95mg, 90μL, 0.35mmol). This mixture was stirred for 48h at room temperature. Water (2mL) was then added and the product was extracted into ether (3 x 15mL). The combined extracts were dried over magnesium sulfate, filtered, and evaporated to give 117mg of a colorless oil. Flash chromatography on silica (10→25% ethyl acetate-hexanes) gave 33.4mg (50%) of **91** as a colorless oil: IR (film) 3300, 2957, 2931, 1494, 1428cm^{-1}; ^{1}H NMR (400MHz, $CDCl_3$) δ 7.70-7.30 (20H, m), 6.55-6.40 (6H, m), 2.77 (1H, m), 2.61 (1H, dd, J=13.9, 2.4), 1.83 (1H, dd, J=13.9, 10.3), 1.13 (9H, s), 1.12 (9H, s), 0.58 (3H, t, J=7.2); ^{13}C NMR (100MHz, $CDCl_3$) δ 149.6, 148.9, 147.7, 147.5, 1335.5, 133.3, 133.2, 131.2, 129.7, 127.7, 127.1, 122.1, 118.2, 117.6, 117.4, 116.1, 115.8, 39.2, 37.7, 32.9, 26.6, 20.3, 19.4, 14.1, 14.0; MS *m/z* 764, 361, 247; Calcd for $C_{49}H_{56}O_8Si$: 764.37188. Found: 764.37220. Anal. Calcd for $C_{49}H_{56}O_8Si$: C, 76.92; H, 7.38. Found: C, 76.49; H, 7.55.

1,2-bis(2-Methoxy-5-t-butyldiphenylsiloxyphenyl)pentane (92)

A solution of **91** (350mg, 0.457mmol) and dimethyl sulfate (460mg, 0.35mL, 3.66mmol) in acetone (50mL) was heated at reflux over potassium carbonate (760mg, 5.49mmol) for 14h. The resulting suspension was diluted with ether (100mL) and quenched with water (50mL). The layers were separated and the water layer was extracted with ether (2 x 25mL). The combined organics were dried over sodium sulfate, filtered, and evaporated to give 426mg of a colorless oil. Flash chromatography of this oil on silica (10% ethyl acetate-hexanes) gave 330mg (91%) of **92** as a colorless oil: IR (film) 3030, 2956, 2931, 1497, 1225, 701cm^{-1}; ^{1}H NMR (400MHz, $CDCl_3$) δ 7.69-7.65 (8H, m), 7.38-7.28 (12H, m), 6.53-6.40 (6H, m), 3.59 (3H, s), 3.47 (3H,

s), 3.11 (1H, m), 2.42 (1H, dd, J=13.3, 7.7), 2.34 (1H, dd, J=13.3, 7.2), 1.30-1.10 (2H, m), 1.08 (9H, s), 1.05 (9H, s), 0.86 (2H, br h, J~7), 0.63 (3H, t, J=7.3); ^{13}C NMR (100MHz, $CDCl_3$) δ 152.1, 152.0, 149.4, 148.7, 135.6, 135.5, 135.2, 133.5, 130.7, 129.7, 127.6, 122.0, 119.0, 116.7, 116.6, 112.0, 110.7, 56.2, 55.8, 37.3, 36.5, 36.3, 26.7, 26.6, 20.3, 19.5, 14.4; MS *m/z* 792, 375, 259, 239, 197, 135; Calcd for $C_{51}H_{60}O_4Si$: 792.4032. Found: 792.4031. Anal. Calcd for $C_{51}H_{60}O_4Si$: C, 76.23; H, 7.62. Found: C, 75.97; H, 7.39.

1,2-bis(2-Methoxy-5-hydroxyphenyl)pentane (89)

To a stirred solution of **92** (16.5mg, 0.021mmol) in tetrahydrofuran (2mL) was added a 1.1M solution of n-butylammonium fluoride in tetrahydrofuran (0.19mL, 0.21mmol) at room temperature. After 1h the mixture was diluted with ether (10mL) and water (2mL). The layers were separated and the water layer was extracted with ether (2 x 10mL). The combined organics were dried over sodium sulfate, filtered, and evaporated to give 18.7mg of a colorless oil. Flash chromatography of this oil on silica (25→50% ethyl acetate-hexanes) gave 6.5mg (99%) of **89** as a colorless oil: IR (film) 3300, 2957, 2932, 1499, 1464, 1222cm^{-1}; ^1H NMR (400MHz, $CDCl_3$) δ 6.65-6.41 (6H, m), 4.90-4.60 (2H, br s), 3.71 (3H, s), 3.59 (3H, s), 3.37 (1H, br p, J=7.4), 2.85 (1H, dd, J=13.4, 6.8), 2.65 (1H, dd, J=13.4, 8.0), 1.52 (2H, m), 1.14 (2H, h, J=7.3), 0.79 (3H, t, J=7.3); ^{13}C NMR (100MHz, $CDCl_3$) δ 152.1, 149.4, 148.8, 137.7, 135.9, 131.0, 117.8, 114.9, 112.7, 112.6, 111.5, 56.6, 56.1, 37.8, 37.1, 36.2, 20.6, 14.1; MS *m/z* 316, 179, 137; Calcd for $C_{19}H_{24}O_4$: 316.1675. Found: 316.1674.

Macrodiolide 88

To a stirred solution of **89** (17mg, 0.054mmol) and triethylamine (17μL, 12mg, 0.12mmol) in methylene chloride (5mL) at -78°C was added **93** (7.0μL,

9.0mg, 0.054mmol). The resulting solution was stirred for 1h at -78°C and quenched with water (5mL). The layers were separated and the aqueous layer was extracted with methylene chloride (2 x 15mL). The combined organics were dried over sodium sulfate, filtered, and evaporated to give 27.5mg of a colorless oil. Flash chromatography of this oil on silica (25% ethyl acetate-hexanes) gave 13.5mg (61%) of **88** as a colorless oil: IR (film) 2959, 2919, 1770, 1750, 1497, 1207cm^{-1}; ^{1}H NMR (400MHz, $CDCl_3$) δ 6.85-6.11 (6H, m), 3.85-3.40 (8H, m), 3.01-2.89(1H, m), 2.85-2.50 (1H, m), 2.20-2.00 (2H, m), 1.70-1.40 (2H, m), 1.35-1.05 (5H, m), 0.95-0.880 (3H, m); ^{13}C NMR (100MHz, $CDCl_3$) δ 167.9, 155.7, 144.3, 143.5, 135.2, 130.7, 123.4, 120.5, 119.1, 118.8, 111.5, 110.5, 55.8, 53.5, 37.8, 37.1, 36.8, 36.3, 22.3, 20.6, 14.0, 11.7; MS *m/z* 412, 316, 233, 179, 137, 97; Calcd for $C_{24}H_{28}O_6$: 412.1886. Found: 412.1885.

Ethylmalonyl Dichloride (93)

A mixture of **90** (10.0g, 75.7mmol) and thionyl chloride (25mL, 40.5g, 0.341mmol) was heated overnight at reflux. The resulting amber solution was concentrated in vacuo and residual thionyl chloride was removed by successive ether addition and evaporation (3 x). The remaining material was distilled to give 9.36g (73%) of **93** as a colorless oil: mp 46-47°C @ 4.0mm/Hg (lit.[44] 76-82°C @ 35mm/Hg); IR (film) 2980, 2943, 1791, 1460cm^{-1}; ^{1}H NMR (400MHz, $CDCl_3$) δ 4.15 (1H, t, J=7.2), 2.16 (2H, p, J=7.3), 1.08 (3H, t, J=7.5); ^{13}C NMR (100MHz, $CDCl_3$) δ 167.6, 73.6, 23.2, 10.8.

Di-2-(trimethylsilyl)ethyl Ethylmalonate (94)

To a stirred solution of 2-trimethylsilylethanol (2.80g, 3.40mL, 23.7mmol) and triethylamine (5.0mL, 3.60g, 35.5mmol) in methylene chloride (20mL) at 0°C was slowly added **93** (2.0g, 3.40mL, 11.8mmol). After stirring for 2h the reaction mixture

was diluted with methylene chloride (50mL) and quenched with water (50mL). The layers were separated and the water layer was extracted with methylene chloride (2 x 50mL). The combined organics were dried over magnesium sulfate, filtered, and evaporated to afford 3.07g (78%) of **94** as a colorless oil: IR (film) 2955, 1750, 1730, 1284, 840cm^{-1}; ^{1}H NMR (400MHz, $CDCl_3$) δ 4.24-4.20 (2H, m), 3.22 (1H, t, J=7.4), 1.92 (2H, p, J=7.4), 1.02-0.94 (7H, m), 0.04 (18H, s); ^{13}C NMR (100MHz, $CDCl_3$) δ 169.6, 63.5, 53.8, 22.2, 17.2, 11.9, -1.6; MS *m/z* 289, 147, 133, 89, 73.

2-(Trimethylsilyl)ethyl Ethylmalonate (95)

A 1.0M solution of tetra-n-butylammonium fluoride in tetrahydrofuran (0.69mL, 0.69mmol) was added to a stirred solution of **94** (231mg, 0.69mmol) at room temperature. After 1h the reaction mixture was diluted with ether (25mL) and a pH4 buffer (10mL, prepared from acetic acid (2.82mL), sodium acetate trihydrate (1.47g) and water (to 300mL)) was added. The layers were separated and the aqueous material was extracted with ether (25mL) and ethyl acetate (25mL). The combined organics were dried over magnesium sulfate, filtered, and evaporated to give 170mg (100%) of **95** as a colorless oil: IR (film) 3300, 2956, 1735, 1716, 1252, 838cm^{-1}; ^{1}H NMR (400MHz, $CDCl_3$) δ 4.25 (2H, m), 3.29 (1H, t, J=7.3), 1.95 (2H, dp, J=7.4, 2.9), 0.99 (5H, m), 0.04 (9H, s); ^{13}C NMR (100MHz, $CDCl_3$) δ 174.9, 169.7, 64.1, 53.2, 22.4, 17.2, 11.8, -1.6; MS *m/z* 177, 133, 89.

Phenoxy Esters 97 and 98

To a solution of **89** (68mg, 0.22mmol) and (50mg, 0.22mmol) and dry acetonitrile (10mL) was added 4-dimethylaminopyridine (58mg, 0.47mmol) and 2-chloro-1-methylpyridinium iodide (**96**, 60mg, 0.24mmol). After stirring for 4h at room temperature the reaction mixture was concentrated in vacuo and subjected to flash chromatography on silica (25% ethyl acetate-hexanes) to afford 40mg (35%) of a

mixture of **97** and **98** as a colorless oil: IR (film) 2957, 1761, 1751, 1498, 1209cm^{-1}; ^{1}H NMR (400MHz, $CDCl_3$) δ 6.88-6.54 (5H, m), 6.28 (1H, d, J=3), 4.30 (2H, br d, J=7.9), 3.74 (3H, 2s), 3.61 (3H, 3s), 3.52-3.40 (2H, m), 2.96-2.59 (2H, m), 2.05 (2H, sept., J=7.0), 1.62-1.51 (2H, m), 1.26-1.12 (2H, m), 1.09-1.02 (3H, m), 0.85-0.79 (3H, m), 0.06 (9H, 2s); ^{13}C NMR (100MHz, $CDCl_3$) δ 169.3, 168.6, 155.6, 151.9, 149.4, 148.9, 143.9, 143.4, 135.5, 135.2, 130.8, 130.1, 130.0, 123.4, 120.8, 118.9, 118.8, 118.6, 118.5, 115.2, 112.8, 112.3, 111.4, 111.3, 110.4, 64.0, 63.9, 56.3, 56.1, 56.0, 55.7, 53.7, 53.6, 53.5, 37.7, 37.3, 36.7, 36.6, 35.9, 35.8, 22.3, 20.6, 20.5, 17.4, 17.3, 14.1, 11.9, 11.8, -1.6; MS (FAB) *m/z* 530, 503, 487, 193; Calcd for $C_{29}H_{42}O_4Si$: 530.2701. Found: 530.2704.

Phenoxy Acids 99 and 100

To a solution of the mixture of **97** and **98** (30mg, 0.056mmol) and tetrahydrofuran (3mL) was added a 1.0M solution of tetra-n-butylammonium fluoride in tetrahydrofuran (110μL, 0.11mmol). After 1h the reaction was quenched with water (5mL). The aqueous mixture was extracted with ether (3 x 20mL). The combined extracts were dried over sodium sulfate, filtered,and evaporated to give 25mg of a colorless oil. Flash chromatography of this oil on silica (25% ethyl acetate-hexanes) gave 9.6mg (38%) of a mixture of **99** and **100** as a colorless oil: IR (film) 3300, 2931, 1756, 1498cm^{-1}; ^{1}H NMR (400MHz, $CDCl_3$) δ 6.80-6.20 (6H, m), 3.75 (3H, 2s), 3.62 (3H, 2s), 3.50-3.38 (2H, m), 2.96-2.71 (2H, m), 2.50 (2H, m), 1.81-1.72 (2H, m),1.60-1.53 (2H, m), 1.28-1.15 (2H, m), 1.07-1.00 (3H, m), 0.86-0.80 (3H, m); ^{13}C NMR (100MHz, $CDCl_3$) δ 173.4, 172.8, 155.5, 152.0, 151.9, 149.3, 148.9, 144.1, 143.6, 135.3, 130.6, 130.0, 123.8, 123.5, 121.3, 120.6, 119.2, 119.1, 119.0, 118.8, 115.4, 112.9, 112.3, 111.4, 111.2, 110.4, 56.3, 56.1, 56.0, 55.7, 37.6, 37.4, 36.6, 36.3, 36.2, 35.9, 35.6, 20.7, 20.6, 18.5, 18.4, 14.1, 13.7, 13.6; MS *m/z* 387, 263, 193.

Bibliography

For bibliographic citations relating to Part I see pp. 30-32.

1. Sutherland, J.K. Fortschr. *Chem. Org. Naturst.* **1967**, *35*, 131.
2. Wijkman, N. *Liebigs Ann. Chem.* **1931**, *485*, 61.
3. Yuill, J.L. *Biochem. J.* **1934**, *28*, 222.
4. Raistrick, H.; Smith, G. *Biochem. J.* **1933**, *27*, 1814.
5. Fritz, W.; Engst, R.; Donath, R. *Nahrung* **1976**, *20*, 539.
6. Webster, J. *Introduction to Fungi*, Cambridge University Press: Cambridge, 1980.
7. Escoula, L.; Henry, G. *Ann. Rech. Vet.* **1975**, *6*, 315.
8. King, A.D.;Booth, A.N.; Stafford, A.E.; Waiss, A.C. *J. Food Sci. (C)* **1972**, *37*, 86.
9. a. Wijkman, N.; Sutter, H. *Liebigs Ann. Chem.* **1935**, *519*, 97.
   b. Wijkman, N.; Sutter, H. *Liebigs Ann. Chem.* **1933**, *505*, 248.
   c. Kraft, K.; Porsch, H. *Liebigs Ann. Chem.* **1936**, *527*, 168.
   d. Kraft, K. *Liebigs Ann. Chem.* **1937**, *530*, 20.
10. Baldwin, J.E.; Barton, D.H.R.; Bloomer, J.L.; Jackman, L.M.; Rodriguez-Hahn, L.; Sutherland, J.K. *Experientia* **1962**, *18*, 345.
11. Robertson, J.M.; Sim, G.A.; Hamor, T.A.; Paul, I.C. *J. Chem Soc.* **1963**, 5502.
12. Baldwin, J.E.; Barton, D.H.R.; Sutherland, J.K. *J. Chem. Soc.* **1965**, 1787.
13. Freudenberg, K.; Lwowski, W. *Liebigs Ann. Chem.* **1955**, *594*, 76.
14. Matell, M. *Arkiv. Kemi* **1952**, *5*, 17.
15. Stork, G.; Tabak, J.M.; Blount, J.F. *J. Am. Chem. Soc.* **1972**, *94*, 4735.
16. Barton, D.H.R.; Sutherland, J.K. *J. Chem. Soc.* **1965**, 1769.
17. Boomer, J.L.; Moppett, C.E.; Sutherland, J.K. *J. Chem. Soc.* **1968**, 588.

18. Griffin, G.W.; Basinski, J.E.; Vellturo, A.F.; *Tetrahedron Lett.* **1960**, 13.

19. Srinivasan, R.;Carlogh, K.H. *J. Am. Chem. Soc.* **1967**, *89*, 4932.

20. Scheffer, J.R.; Wostradowski, R.A. *J. Chem. Soc., Chem. Commun.* **1971**, 144.

21. Oppolzer, W. *Acc. Chem. Res.* **1982**,*15*, 35.

22. Laursen, R.D.; Shen, W.-C.; Zahka, K.G. *J. Med.Chem.* **1971**, *14*, 619.

23. Corey, E.J.; Wat, E.K.W. *J. Am. Chem Soc.* 1967, *89*, 2757.

24. a. Ledwith, A.; Kricka, L.J. *J. Chem. Soc., Perkin Trans. 1* **1973**, 294.

b. Green, J.; McHale, D.; Marcinkiewicz, S.; Mamalis, P.;Watt, P.R. *J. Chem.Soc.* **1959**, 3362

25. Kagan, H.B.; Girard, P.; Namy, J.L. *J. Am. Chem. Soc.* **1980**, *102*, 2693.

26. Sutherland, J.K.; Huq, E. *Chem. Eng. Res. Bull. (Dacca)* **1978**, *2*, 29.

27. Vaughan, W.R.; Milton, K.M. *J. Am. Chem. Soc.* **1951**, *73*, 5497.

28. Whitesides, G.M.; SanFilippo, J.; Casey, CP.; Panek, E.J. *J. Am. Chem. Soc.* **1967**, *89*, 5302.

29. Webb, I.D.; Borcherdt, G.T. *J. Am. Chem. Soc.* **1951**, *73*, 2654.

30. Gorbers, C.F.; Labuschagne, J.M.; Meyer, C.J.; Scheider, D.F. *J. Chem. Soc., Perkin Trans. 1* **1973**, 2016.

31. Dreiding, A.S.; Martin, R.; Chapleo, C.R.; Svanholt, K.L. *Helv. Chim. Acta* **1976**, *59*, 2724.

32. Boeckman, R.K.; Ko, S.S. *J. Am. Chem. Soc.* **1982**, *104*, 1033.

33. Marshall, J.A.; Delthoff, B.S. *Tetrahedron Lett.* **1986**, *27*, 4873.

34. Weinreb, S.M.; Tschaen, D.M.; Turos, E. *J. Org. Chem.* **1984**, *49*, 5058.

35. Weiler, L.; Sum, F.W. *Tetrahedron Suppl.* **1981**, *9*, 303.

36. Gold, E.H.; Ginsburg, D. *J. Chem. Soc. (C)* **1967**, 15.

37. Corey, E.J.; Kim, C.U.; Takeda, M. *Tetrahedron Lett.* **1972**, 4339.

38. Sarma, A.S.; Chattopodhyay, P. *J. Org. Chem.* **1982**, *44*, 1727.

39. Catagnoli, N.; Jacob, P.; Callery, P.S.; Shulgin, A.T. *J. Org. Chem.* **1976**, *41*, 3627.

40. Shulgin, A.T.; Dyer, D.C. *J. Med. Chem.* **1975**, *18*, 1201.

41. McOmie, J.F.W.; Watts, M.L.; West, D.E. *Tetrahedron* **1968**, *24*, 2289.

42. Cookson, R.C.; Cox, D.A.; Hudec, J. *J. Chem. Soc.* **1961**, 4490.

43. Mukaiyama, T.; Usui, M.; Shimada, E.; Saigo, K. *Chem. Lett.* **1975**, 1048.

44. Galimberti, P. *Gazz. Chim. Ital.* **1942**, *72*, 125.

45. Mukaiyama, T.; Usui, M.; Saigo, K. *Chem. Lett.* **1976**, 49.

46. Gerecs, A. *Friedel-Crafts and Related Reactions*, vol. 3, pp. 499-533. Ed. G. Olah. New York: Interscience Publishers, 1963-64.

47. Blatt, A.H. *Org. Reactions* **1942**, *1*, 342.

48. Martin, R. *Bull. Soc. Chim. Fr.* **1974**, 983.

49. Ogata, Y.; Tabuchi, H. *Tetrahedron* **1964**, *20*, 1661.

50. Bellus, D.; Hrdlovic, P. *Chem. Rev.* **1967**, *67*, 599.