The Art of Innovation in Organic Chemistry: Synthetic Efforts toward the Phomoidrides

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I. Introduction

"Doing science at the highest, most creative level is a bit like playing jazz. One has to be disciplined, yes, but also open, flexible, ready to abandon an idea and pick up a new one when Nature thrusts it upon one." — J. A. Berson[1]

Since initial reports of the isolation of phomoidrides A and B,[2,3] many synthetic chemists have traveled the arduous road toward their total syntheses.[4−6] Because of their biological activities and wide array of intriguing structural features, four total syntheses and at least 18 advanced synthetic approaches have been developed in recent years. In support of these efforts, synthetic chemists have been inspired to invent novel synthetic methods to face the formidable chemical challenges posed by the phomoidrides. Herein will be reviewed these total syntheses and synthetic approaches, as well as the newly developed chemistry that represents their progeny.

A. Isolation and Characterization

Detailed accounts describing the biological testing and structure elucidation of the phomoidrides were published by Pfizer researchers in 1997.[7,8] These unusual secondary metabolites, isolated from an unidentified fungus obtained from the twigs of a juniper tree in Dripping Springs, Texas, were found to inhibit the enzymes Ras farnesyl transferase and squalene synthase (SQS) and to possess structural and stereochemical features never before observed together in a single compound: a bridgehead double bond contained in a bicyclo[4.3.1]deca-1,6-diene carbon framework,[9] a quaternary center held in a caged spirolactone, a maleic anhydride moiety, and two pendant olefinic side chains. The presence of a nine-membered ring with an affixed maleic anhydride functionality led the Pfizer scientists to classify this molecule within the nonadride family, which includes glaucanic acid (**13**), glauconic acid, byssochlamic acid, and others.[10,11] On the basis of the producing organism (likely a sterile *Phoma* species) and their inclusion in the nonadride class, these molecules (Figure 1) were given the names phomoidride A (CP-225,917, **1**) and phomoidride B (CP-263,114, **2**).[5]

Later, during synthetic studies directed at the total syntheses of **1** and **2** (see Section II.B.4), Danishefsky and co-workers isolated the 7*R* isomer of phomoidride B (**4**) from fermentation broths of ATCC 74256, the producing organism of **1** and **2**.[12] They then went on to characterize this compound, along with a synthetic sample of the 7*R* isomer of phomoidride A (**3**). The Sulikowski group was eventually able to isolate **3** from ATCC 74256 fermentation broths and named compounds **3** and **4** phomoidrides C and D, respectively.[13] To date, no measurements of the biological properties of **3** and **4** have been reported.

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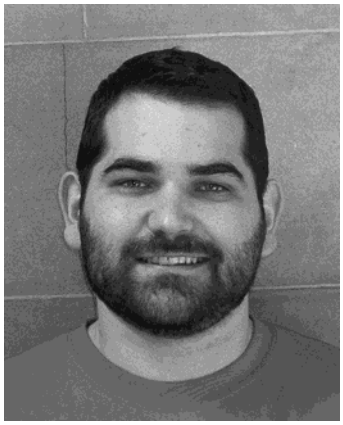
David A. Spiegel was born in New York City in 1973. He grew up in Teaneck, New Jersey, and attended Harvard University where he conducted research under the guidance of Professor Yoshito Kishi. He is currently a student in Yale University's M.D./Ph.D. program where he is pursuing graduate studies in the laboratory of Professor John L. Wood toward the total syntheses of the phomoidrides. After he graduates from Yale, he will move back to Harvard University to pursue postdoctoral studies under the guidance of Professor Stuart L. Schreiber. His research interests focus on the applications of organic chemistry to problems in complex molecule synthesis, biology, and medicine.

Jón Tryggvi Njardarson was born in Akranes, Iceland. He obtained his Bachelor's degree in chemistry from the University of Iceland, where he worked in the laboratory of Jón K. F. Geirsson. He then moved to Yale University to pursue graduate studies in chemistry and joined the research group of John L. Wood. His thesis research focused on the total synthesis of the then recently disclosed natural products CP-225,917 (Phomoidride A) and CP-263,114 (Phomoidride B). After he obtained his Ph.D., he moved to New York City to work as a General Motors Cancer Research Scholar under the guidance of Professor Samuel J. Danishefsky at the Sloan-Kettering Institute for Cancer Research. His work at Sloan-Kettering has focused on the total synthesis of natural products, in particular the epothilones and migrastatin. His research interests include the development of new synthetic methods and their application in the construction of biologically important natural products.



Ivar M. McDonald was born in Brooklyn, Connecticut, in 1977. After he obtained his B.A. in chemistry from Boston University in 1999, he joined the laboratory of Professor John L. Wood at Yale Univeristy. He is currently pursuing Ph.D. research focused on the total synthesis of the phomoidrides.

John L. Wood was born on December 4, 1961 in Keokuk, Iowa. He received a B.A. degree from the University of Colorado in 1985 and a Ph.D. from the University of Pennsylvania in 1991 under the direction of Amos B. Smith, III. In 1991, he moved to Harvard University as an American Cancer Society postdoctoral fellow and continued studying natural products synthesis in the laboratories of Stuart Schreiber. He joined the faculty at Yale University in 1993 as an Assistant Professor and was promoted to Full Professor in 1998. The major focus of Professor Wood's research is synthetic organic chemistry. Of primary emphasis is the design of innovative solutions to problems in natural product synthesis. Professor Wood has received numerous awards and honors including a Camille and Henry Dreyfus New Faculty Award in 1993, a Bristol-Myers Squibb Research Award in 1997, an Alfred P. Sloan Fellowship in 1997, and research awards from the Bristol-Myers Squibb Foundation and the Yamanouchi USA foundation in 1998. In 2000, Professor Wood received a Merck Faculty Award, and in 2001, he was awarded The Kitasato Institute's Microbial Chemistry Medal.

B. Phomoidride Rendering

Because of their topologically complex structures and/or the wide range of synthetic disconnections employed in their syntheses, the phomoidrides have been rendered in a number of different ways. While these illustrations all represent the same structure, it is instructive to observe how each depiction lends itself to certain synthetic disconnections and not to others. Figure 1 contains the naturally occurring enantiomers of phomoidrides A−D drawn from three different perspectives.[14] Carbons are labeled using phomoidride numbering in order to assist in comparison of synthetic schemes throughout the text.

C. Biological Activity

Phomoidrides A and B have intriguing biochemical properties. They have been shown in vitro to inhibit both the enzymes SQS and Ras farnesyl transferase.[8,18] For this reason, **1** and **2** are thought to be attractive lead structures for the development of cholesterol-lowering or anticancer agents.

1. Antihypercholesterolemic Properties

Cardiovascular disease (CVD) has been the leading cause of death in the United States in every year

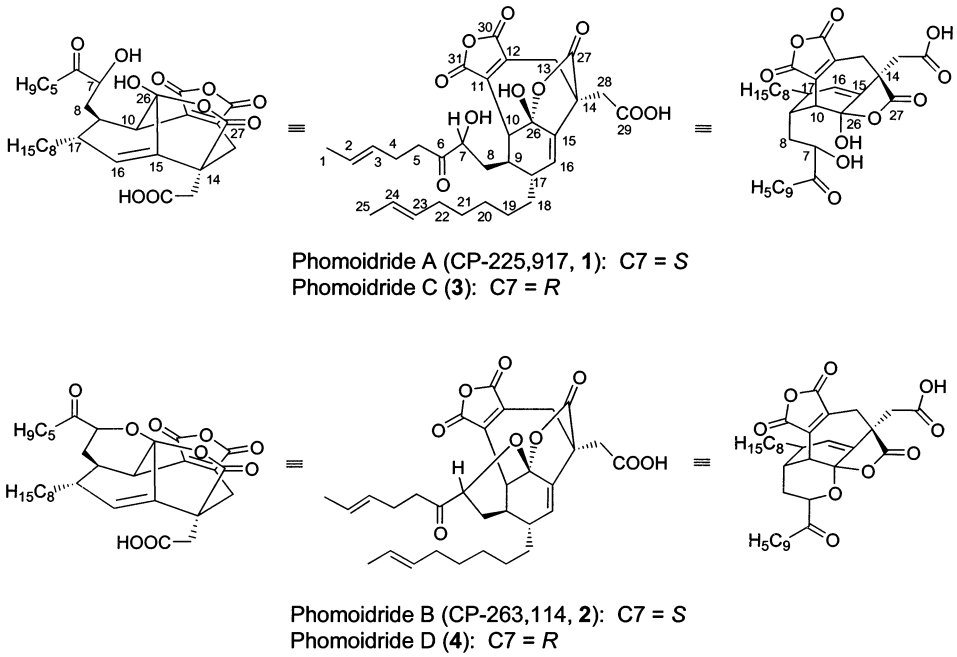


Figure 1. The phomoidrides.[15−17]

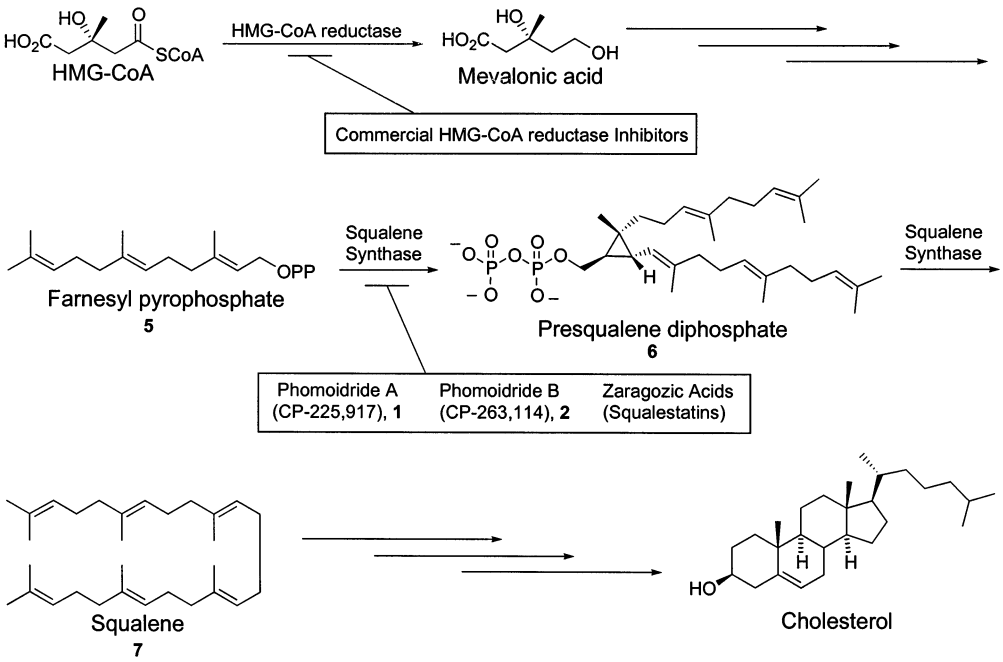


Figure 2. Simplified depiction of the cholesterol biosynthetic pathway and the sites of action of its inhibitors.

since 1919;[19,20] in the year 2000 alone, over 878,000 people died from diseases of cardiac or vascular origin, a number greater than the next four leading causes combined.[21] Because numerous studies have established an unequivocal link between levels of serum cholesterol and CVD[22,23] and, in humans, upward of 70% of serum cholesterol is derived from de novo biosynthesis,[24] inhibitors of enzymes in the sterol biosynthetic pathway have served as useful therapies in preventing such diseases.[25] To this end, research efforts in industrial settings have focused on designing pharmaceutical agents, referred to as statins, that inhibit the enzyme HMG-CoA reductase (see Figure 2; HMG-CoA → mevalonic acid).[26] The sales of such agents have turned the statins into multibillion dollar therapeutics.

While HMG-CoA reductase catalyzes the rate-limiting step in cholesterol biosynthesis, SQS promotes the first committed step of this process.[27] It therefore represents a potentially useful target in treating hypercholesterolemia.[24] However, to date, no commercially available therapeutics that target this enzyme have been developed. For this reason, large-scale industrial programs have been initiated to discover SQS inhibitors. The phomoidrides and zaragozic acids represent such discoveries and they will hopefully serve as lead compounds toward the development of clinically useful agents.

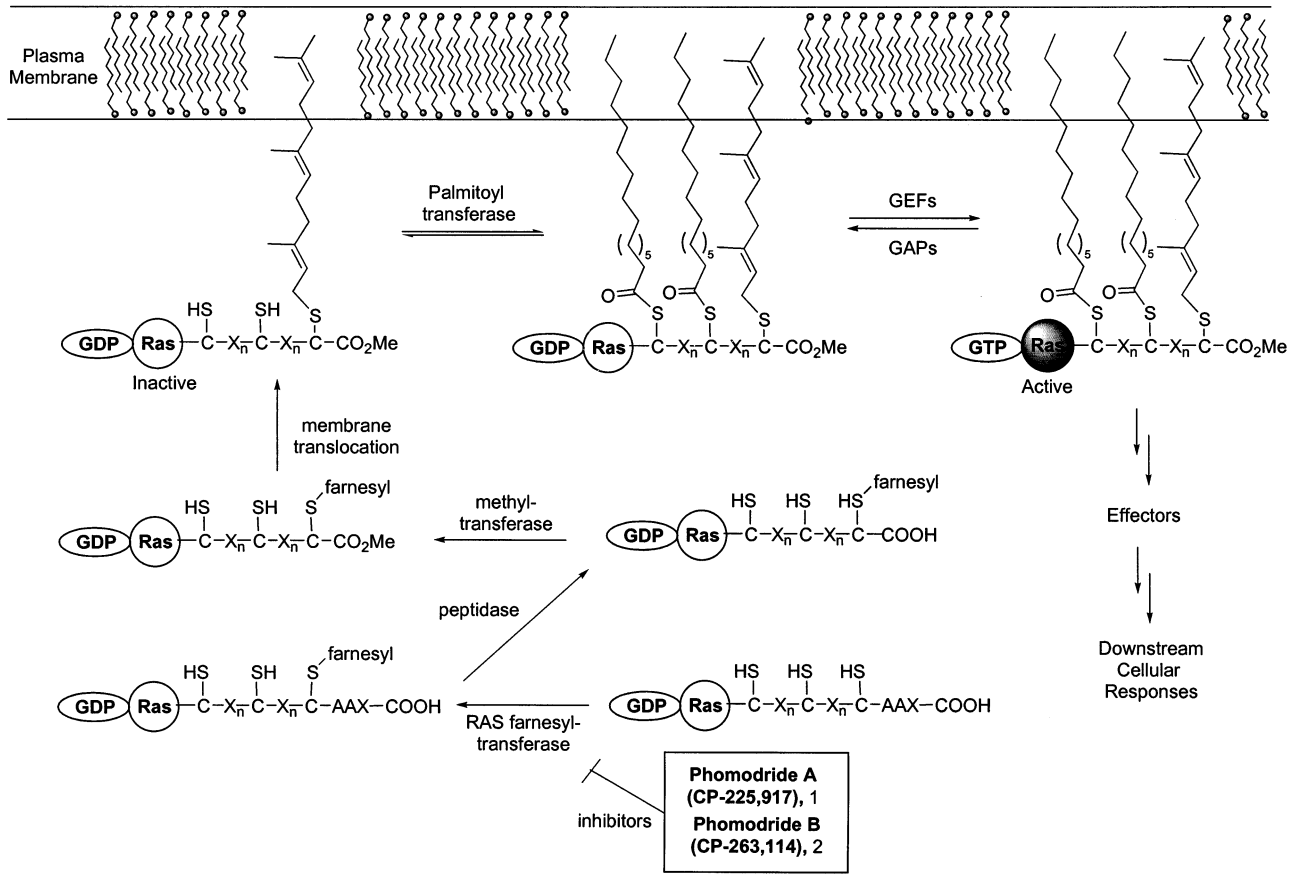


Figure 3. Simplified depiction of the posttranslational processing and activation of H-Ras and its inhibition by phomoidrides A and B (**1** and **2**).[35] GEFs, guanine nucleotide exchange factors; GAPs, guanine triphosphatase activating proteins; GDP, guanosine diphosphate; GTP, guanosine triphosphate.

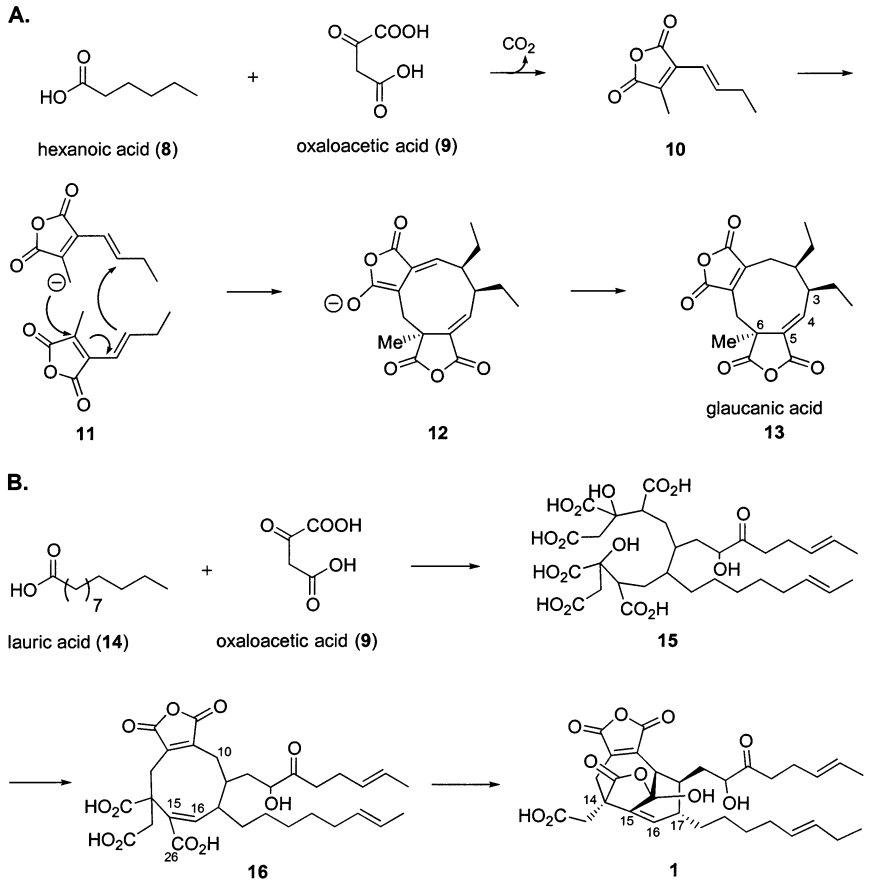
The mechanism by which SQS catalyzes the production of squalene (**7**) has been thoroughly studied[28] and is depicted in Figure 2. In the first step, two molecules of farnesyl pyrophosphate (FPP, **5**) are condensed to form presqualene diphosphate (**6**), which is then directed by SQS to undergo a reductive rearrangement to **7**. Initial experiments have demonstrated that **1** and **2** exert their effects on the first half-reaction catalyzed by SQS (**5** → **6**).[8] In addition, these studies have determined that SQS inhibition by the phomoidrides is reversible and of the mixed noncompetitive type with respect to the substrate (**5**). Taken together, these data are consistent with a model in which **1** and **2** are capable of reversibly occupying FPP binding sites in the free enzyme or in the enzyme bound to a single FPP molecule. Further mechanistic studies are reported to be in progress.[8]

2. Ras Biology and Anticancer Activity

Mutations in the Ras oncogene have been found in up to 30% of all human cancers.[29] For this reason, the Ras oncoprotein is considered to be of great importance as a target in the search for anticancer agents.[30,31] Common oncogenic mutations in Ras produce a constitutively active protein. It is fully capable of transducing intracellular signals but does so in an unregulated fashion because it is unable to hydrolyze guanosine triphosphate (GTP).[32] Because all forms of Ras must be processed extensively by a series of enzymes in order to transduce their mitogenic signals, interfering with Ras processing is an effective method for curtailing the function of aberrant forms of the protein.[33,34]

The Ras processing and activation pathway has been studied in great detail and is depicted in simplified form in Figure 3. The first step in the sequence involves the transfer of a farnesyl group by the enzyme Ras farnesyl transferase to a terminal cysteine in the Ras protein. This cysteine must be contained within a stretch of four C-terminal amino acid residues possessing the sequence CAAX (called a "CAAX box"). Peptidase cleavage of the tripeptide (AAX), which neighbors the newly modified cysteine, followed by methylation of the farnesyl−cysteine carboxylate by a methyltransferase enzyme, initiates translocation of the protein to the cell membrane. Further lipidation with palmitoyl groups on additional C-terminal cysteine residues allows membrane localization to take place. Once attached to the membrane, the inactive guanosine diphosphate (GDP)-bound Ras protein becomes active via the exchange of protein-bound GDP for GTP with the help of guanine−nucleotide exchange factors (GEFs). Subsequent GTP hydrolysis, induced by GTPase-activating proteins (GAPs), shuts off Ras-mediated signaling and returns the protein to its inactive state. Activating mutations in Ras found in human cancers all prevent this GAP-induced GTP hydrolysis and serve to keep the Ras oncoprotein permanently in the "on"

Scheme 1. Proposed Nonadride Dimerization Mechanisms



state, allowing it to stimulate cellular proliferation continuously.[30,31]

If Ras is not lipidated, and therefore not tethered to the plasma membrane, it cannot perform its intracellular functions. Therefore, by interrupting any of the steps by which the Ras protein is post-translationally modified, therapeutics can prevent the growth of cancers containing the Ras oncoprotein. As inhibitors of Ras farnesyl transferase, the phomoidrides could play a vital role as lead structures for the design of novel anticancer agents.

D. Biosynthetic and Degradative Studies of the Phomoidrides

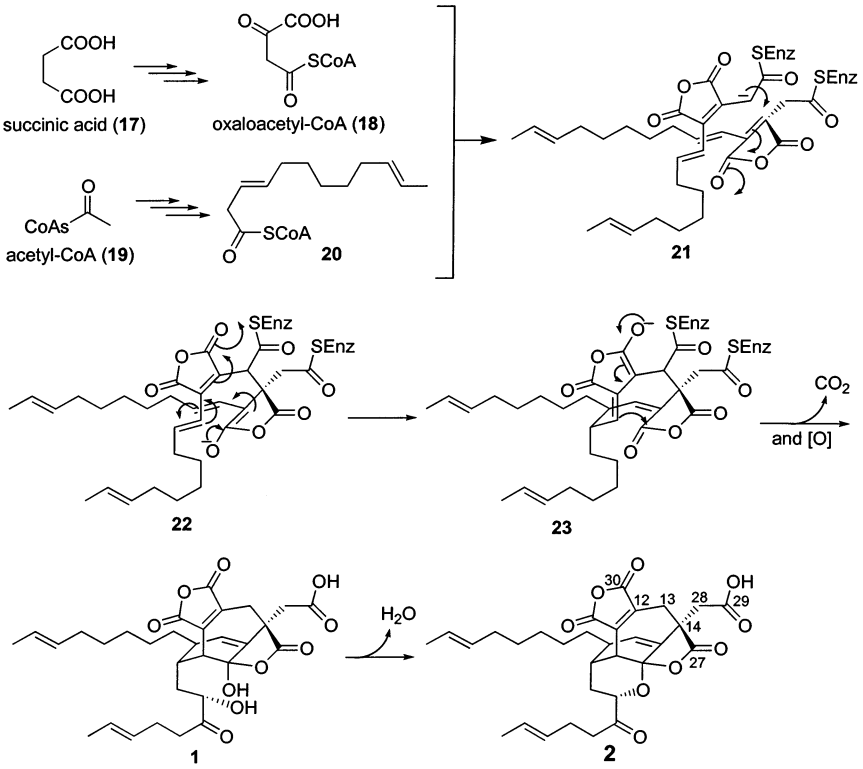
Various research groups have studied the biosyntheses of members of the nonadride family, and current biosynthetic proposals toward the phomoidrides arise directly from some of this work. Studies performed in the Barton and Sutherland groups on the biosyntheses of glaucanic acid (**13**) and glauconic acid have provided evidence that these nonadride natural products are produced in vivo by the head-to-head dimerization of a nine-carbon anhydride (**10** → **13**; Scheme 1A).[11,36−39] This anhydride, in turn, is thought to arise biosynthetically from the condensation of hexanoic acid (**8**) and oxaloacetic acid (**9**).

In the second isolation report of the phomoidrides,[7] Kaneko and co-workers draw a direct analogy to this early work of Barton and Sutherland by proposing a series of biosynthetic disconnections tracing the phomoidrides back to lauric acid (**14**) and **9** (Scheme 1B). These researchers speculate a head-to-head dimerization of two 16-carbon units to provide a maleic anhydride-containing nine-membered ring (**16**) via a stepwise mechanism proceeding through intermediate **15**. Homoenolate attack of the C26 carboxylate by C10 in **16** and tautomerization to form a pseudoacid leads to phomoidride A (**1**).

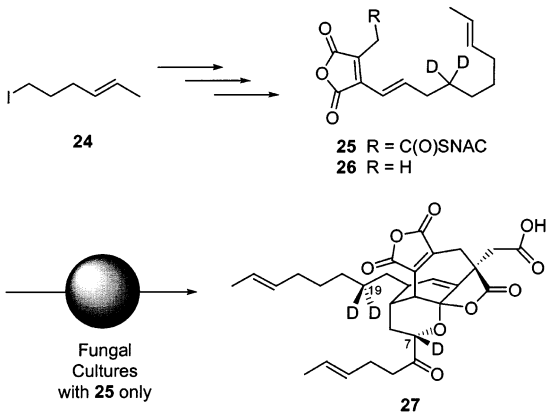
In their initial investigations into phomoidride biosynthesis, Sulikowski and co-workers point out that two questions remain unanswered by Kaneko's model.[40] First, it is not predictive of the (*Z*)-geometry in the phomoidride C15−C16 double bond. Unlike in **1** and **2**, the C4−C5 double bond in **13** is of the (*E*)-geometry, as is that between C15 and C16 in Kaneko's proposed intermediate (**16**). Second, the relative stereochemistry between C14 and C17 in **1** is opposite to that between the analogous centers in **13** (C6 and C3).

To clarify this apparent discrepancy, the Sulikowski group proposes a modification of Kaneko's ideas, drawing an analogy to polyketide and fatty acid biosynthesis (Scheme 2).[40] They suggest that two 16-carbon anhydrides are covalently attached to an enzyme via a thioester linkage (**21**) and are thus preorganized to undergo a stepwise dimerization process to yield the phomoidride skeleton. This hypothesis was investigated using ^{13}C-labeling studies. By incubating fungal cultures with ^{13}C-labeled succinic acid and acetyl-CoA derivatives, Sulikowski demonstrated that carbons C12−C14 and C27−C30 in **2** all originated from carbons found in succinic acid, and the remaining carbons could be traced back

Scheme 2. Sulikowski's Proposed Biosynthesis of Phomoidrides



Scheme 3. Sulikowski's Deuterium Labeling Experiments



to acetyl-CoA (**19**). These results supported their biosynthetic route, in which anhydrides **21** are formed from the condensation of a 12-carbon piece derived from **20** and the 4-carbon-containing oxaloacetyl-CoA (**18**). In turn, **18** is known to be derived biosynthetically from succinic acid (**17**), and **20** is postulated to originate from **19**. The proposed sequential Michael additions (**21** → **22** and **22** → **23**) followed by Dieckmann type cyclization, loss of CO_2, and oxidation to give **1** provide a reasonable mechanism for the formation of the phomoidride carbocyclic core but do not provide direct evidence for any of the individual steps in the pathway.

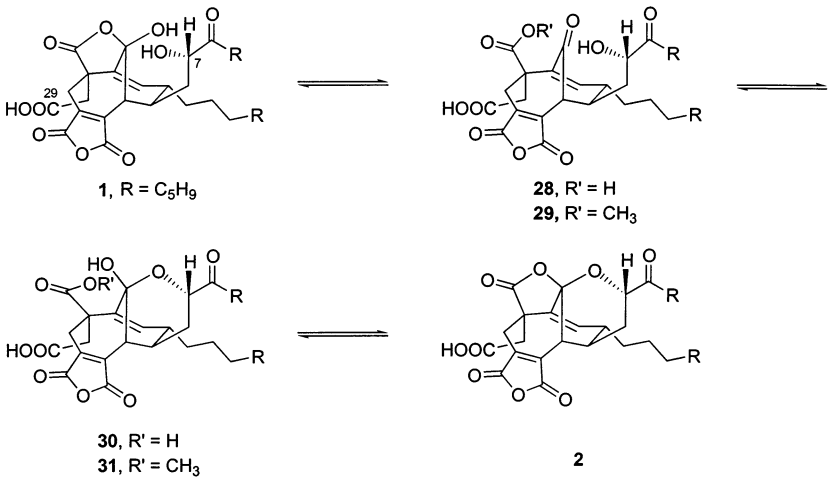
In a later paper, Sulikowski went on to test the proposed decarboxylative homodimerization mechanism through deuterium-labeling studies with maleic anhydride **25** (Scheme 3).[41] In these experiments, **25** was synthesized starting with hexenyl iodide **24** in 15 steps and fed to cultures of ATCC 74256, the producing fungus of the phomoidrides. Isolates of phomoidride B from these fungal broths (**27**) revealed deuterium incorporation at C7 and C19 of the natural product as detected by ^{2}H NMR spectroscopy and confirmed by electrospray mass spectrometry. Feeding decarboxylated anhydride **26** to ATCC 74256 cultures failed to yield any deuterium incorporation into phomoidride isolates. These results are consistent with the proposed biosynthetic pathway depicted in Scheme 2.

E. Interconversion between Phomoidrides A and B

In the paper that describes the initial isolation and characterization of phomoidrides A and B (**1** and **2**), Kaneko and colleagues observed that compound **1** could be converted into **2** on treatment with catalytic methanesulfonic acid,[7] but the reverse transformation did not occur. On this basis, they proposed that the formation of **2** could be accounted for by a cyclodehydration of the hydroxy-hemiacetal contained in **1**. Later on, it was demonstrated by the Nicolaou group that treatment of the closed structure (**2**) with LiOH could refurnish the acetal-opened phomoidride A (**1**).[42] Therein, the Nicolaou group proposed a mechanistic model for this conversion, which necessarily involved a free carboxylate at C29. However, the Danishefsky group later observed that this acetal ring-opening process did not appear to depend on the presence of the free carboxylate at C29, calling Nicolaou's mechanism for the interconversion into question.[12]

Sulikowski contributed to solving this debate by carrying out hydrolysis experiments in basic methanol, which allowed for the isolation of ring-opened

Scheme 4. Sulikowski's Mechanism for Phomoidride Interconversion



intermediate **29** (Scheme 4).[13] It was reasoned that this intermediate was formed via lactone opening of **2** to **31** followed by ring-chain tautomerization. Making the analogy to the LiOH case initially observed by the Nicolaou group, it was hypothesized that basic hydrolysis of **2** could cause its unraveling to intermediate **30**, which could then reorganize to phomoidride A (**1**) by way of open chain ketone **28**. Similarly, acid-catalyzed ring closure of **1** was envisioned to proceed through intermediate **28** via cyclization to **30** followed by lactonization to yield **2**. It was further proposed that the epimerization of C7 in **1** to yield phomoidride C might proceed via cyclic tautomer **30** to yield the sterically less congested exo orientation of the C7 side chain with respect to the bicyclic framework.

F. Epimerization at the C7 Stereocenter

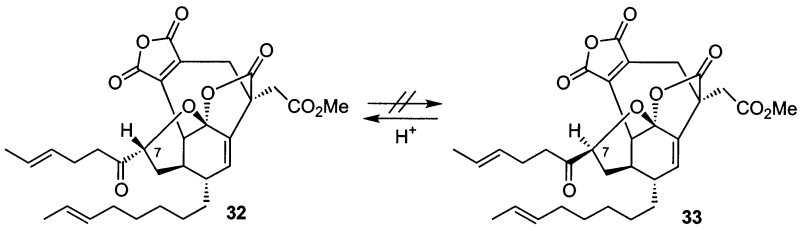
The Danishefsky group first isolated a naturally occurring phomoidride epimeric to **2** at C7 during their attempts to convert synthetic material carrying the 7*R* configuration (**32**) into naturally-derived material with the 7*S* configuration (**33**).[12,13,43] In the process of these epimerization studies, the Danishefsky group uncovered useful information regarding the stereochemical preference at this center (Scheme 5). For example, conversion of material from the 7*S* to the 7*R* configuration (**33** → **32**) occurred readily and was attended only by slight decomposition, while epimerization in the reverse direction could not be affected under any conditions. These results suggested that compounds containing the *R* configuration at C7 represent the thermodynamically favored epimeric series. During the process of isolating natural material, the Danishefsky group recovered fungal-derived phomoidride A that did indeed possess the *R* configuration at C7.

These observations made by the Danishefsky group were recently corroborated by Sulikowski and coworkers, who demonstrated that both epimers of the ring-opened and ring-closed phomoidrides could be isolated from fungal cultures.[13] It was further determined in these studies that the relative production ratios of these four compounds were greatly dependent upon pH with **1** and **2** being the major isolates in all cases. Compounds **3** and **4**, epimeric at C7 to **1** and **2**, respectively, were named phomoidrides C and D.

G. Scope of the Review[44]

This review aims to be comprehensive in its coverage of published total syntheses and synthetic approaches toward the phomoidrides. Also, it provides highlights of the novel chemistry developed during this process. Completed total syntheses are listed first (Section II.B), and in this section, the routes are presented in the order in which they were published. When a particular research group disclosed multiple publications, only those that presented routes leading to completed total syntheses are described in detail. Synthetic approaches that have not yet resulted in completed total syntheses are described in Section II.D. This section is organized by key disconnection. For laboratories that have published papers describing multiple generations of an approach, only the most advanced is described in detail. However, references are provided for the earlier versions. The reader is encouraged to utilize these citations to arrive at a more detailed understanding of researchers' thought processes. Finally, throughout the re-

Scheme 5. Attempted C7 Epimerization



view, "highlights" of newly developed chemistry inspired by the synthetic efforts are provided. These sections are brief and are meant to serve merely as introductions to highlighted chemistry. References are provided for readers who are interested in learning more about these methods.

II. Synthetic Studies

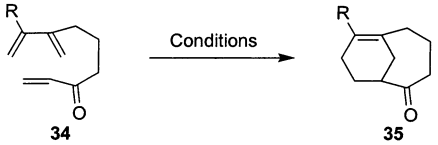
A. Prior Efforts toward the Bicyclo[4.3.1]-deca-1,6-diene Core

Before the isolation and characterization of the phomoidrides, numerous efforts had been initiated toward the syntheses of bicyclic systems containing bridgehead double bonds. Early studies in this area were those of Shea. His fascination with strained olefins led him to study the type II intramolecular Diels−Alder reaction (type II IMDA) in the construction of [*n*.3.1] bridgehead alkenes.[45−51] Scheme 6 details the evolution in the reaction conditions for trienes **34**. Shea first explored using flash vacuum pyrolysis (entry 1), but he later found that the cycloaddition could be effected by heating in refluxing xylenes (entry 2), or by employing Lewis acid catalysis at ambient temperatures (entry 3).

Subsequent studies of bridgehead olefins such as **35** were quite informative. As predicted by Bredt and others,[53,54] the strain of the bridgehead double bond was found to be related to the number of carbons in the bicyclic bridge.[9] For example, the double bond in bicyclo[3.3.1]nonene is approximately 10^6 times more reactive toward electrophiles than corresponding unstrained trisubstituted counterparts.[45] The strain of this bridgehead double bond decreases rapidly with increases in ring size. Bicyclo[4.3.1] systems experience a substantial amount of torsional distortion, which results in decreases in π-system overlap and pyramidalization of the sp^2-hybridized carbons in the olefin. This trend is thought to give rise to the increased reactivity of these species.[48]

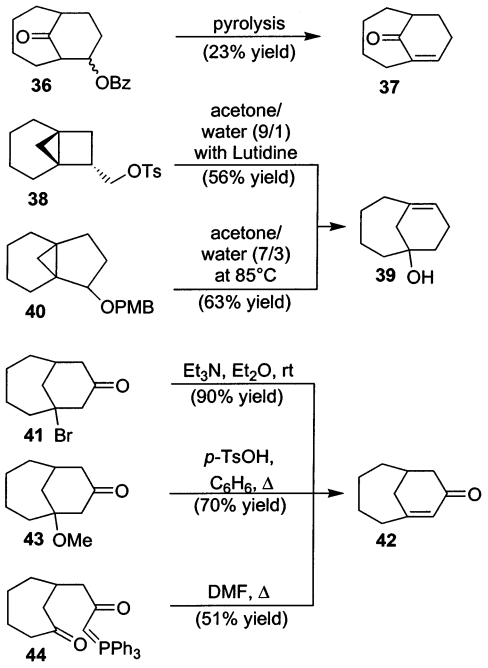
Other approaches toward the bicyclo[4.3.1]decene skeleton are depicted in Scheme 7. These include Wells' pyrolysis of a secondary benzoate (**36** → **37**),[55] a rearrangement discovered by Gassman in his solvolysis studies of bridgehead cyclopropane derivatives (**38** → **39** and **40** → **39**),[56,57] House's β-elimination of a tertiary bromide and an alkoxide (**41** → **42** and **43** → **42**),[58] and Bestmann's intramolecular Wittig olefination (**44** → **42**).[59] Some of these methods

Scheme 6.[52] Evolution of Shea's Approaches to the Bicyclo[4.3.1] Core

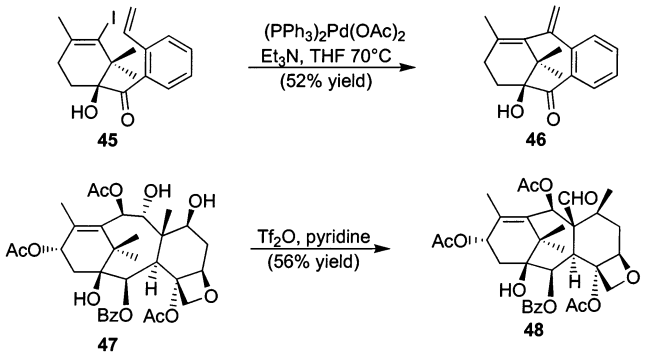


Entry	R	Solvent	Temp. (°C)	Additive	Yield (%)	Ref.
1	H	FVP	398	None	80	46
2	H	Xylenes	201	None	57	49
3	Me	CH_2Cl_2	25	Et_2AlCl	70	50

Scheme 7. Approaches to the Bicyclo[4.3.1] Core



Scheme 8. Unexpected Syntheses of the Bicyclo[4.3.1] Core



are quite high yielding and have paved the way for synthetic efforts directed at the phomoidrides (see below).

Interestingly, synthetic efforts directed at Taxol's bicyclo[5.3.1]undecene core have provided two routes toward the bicyclo[4.3.1] ring system (Scheme 8). For example, Danishefsky's attempted Heck ring closure of compound **45** resulted in the formation of bridgehead alkene **46**.[60] Researchers at Abbott Laboratories observed an unexpected skeletal ring contraction to form **48** when taxol precursor **47** was treated with triflic anhydride.[61]

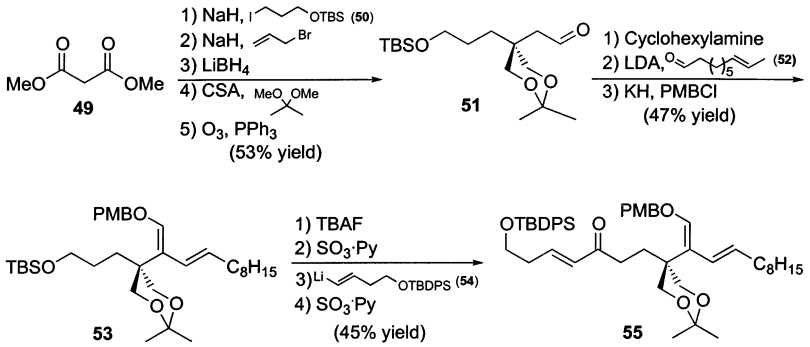
B. Completed Total Syntheses

"The journey to the CP molecules required an unrelenting quest through a synthetic labyrinth endowed with countless obstacles, yet filled with numerous hidden treasures." — K. C. Nicolaou[42]

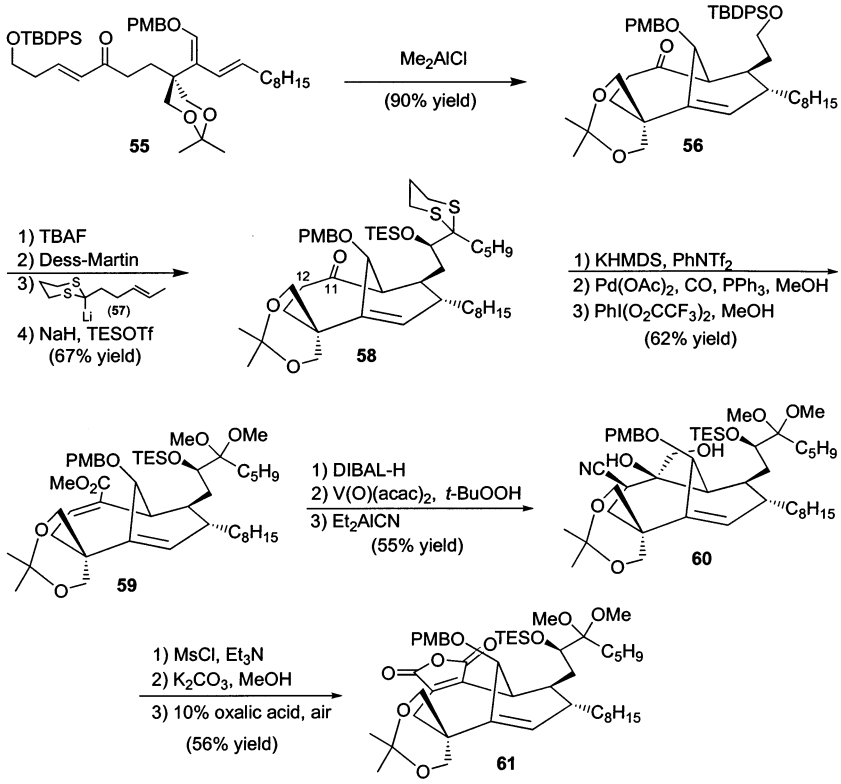
1. Kyriacos C. Nicolaou and Colleagues

The Herculean efforts of the synthetic community toward the total syntheses of phomoidrides A and B have culminated in four completed total syntheses.

Scheme 9. Construction of the Diels–Alder Precursor



Scheme 10. Cycloaddition and Anhydride Formation



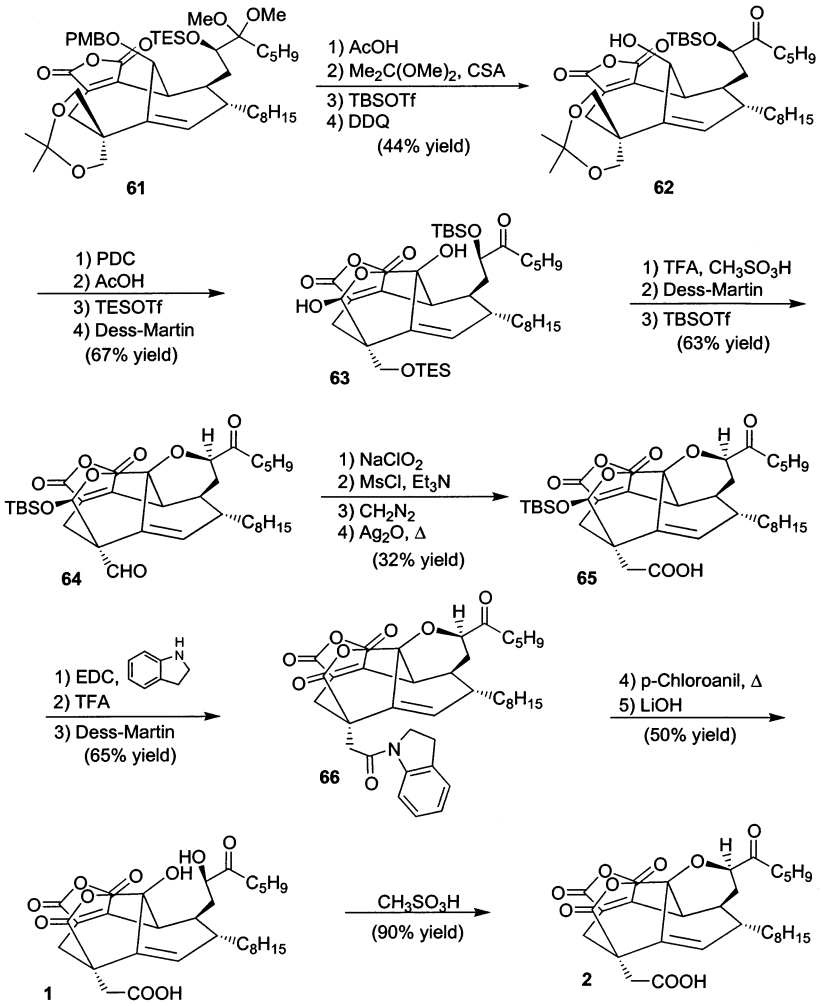
The first of these was published by Nicolaou and coworkers at Scripps[15,42,62–70] and incorporates as its key step a type II IMDA reaction to form the phomoidrides' bicyclo[4.3.1]decene core. Other noteworthy aspects of the approach include a unique tandem sequence to form the maleic anhydride, as well as an Arndt–Eistert homologation to elaborate the C14 quaternary center. Nicolaou's synthesis also gave rise to a number of novel chemical methods. These include two new one-carbon homologation methods[71,72] and a range of new applications for iodine(V)-mediated oxidation chemistry.[73–81]

Nicolaou's total synthesis commenced with the alkylation of commercially available dimethyl malonate (**49**; Scheme 9) with iodide **50** and allyl bromide. The two esters were fully reduced, and the resulting diol was protected as its acetonide. Subsequent ozonolysis of the allyl group revealed aldehyde **51**. Next, the requisite diene for the IMDA reaction was assembled. Reaction of the cyclohexyl enamine of **51** with aldehyde **52** provided the corresponding enone, which was further reacted with potassium hydride and *para*-methoxybenzyl chloride to give diene **53** as the major product. Finally, deprotection of the primary TBS ether, oxidation to the aldehyde, addition of vinyllithium reagent **54**, and reoxidation to the α,β-unsaturated ketone completed the assembly of Diels–Alder precursor **55**.

With **55** in hand, Nicolaou was ready to attempt the crucial Lewis acid-catalyzed type II IMDA reaction. As anticipated, triene **55** readily underwent the cycloaddition (Scheme 10) in high yield to give the bicyclo[4.3.1]decene core (**56**). The primary silyl ether was then deprotected, oxidized to the corresponding aldehyde, reacted under umpolung conditions with lithio dithiane **57**, and protected to provide compound **58**. This incorporates the C1 to C6 side chains found in the phomoidrides.

The Nicolaou group's next task was to transform the sterically hindered C11–C12 α-methylene ketone in **58** into the desired maleic anhydride unit. This problem required that the investigators develop an innovative solution. The sequence began with conversion of the ketone function in **58** into its correspond-

Scheme 11. Completion of the Total Synthesis

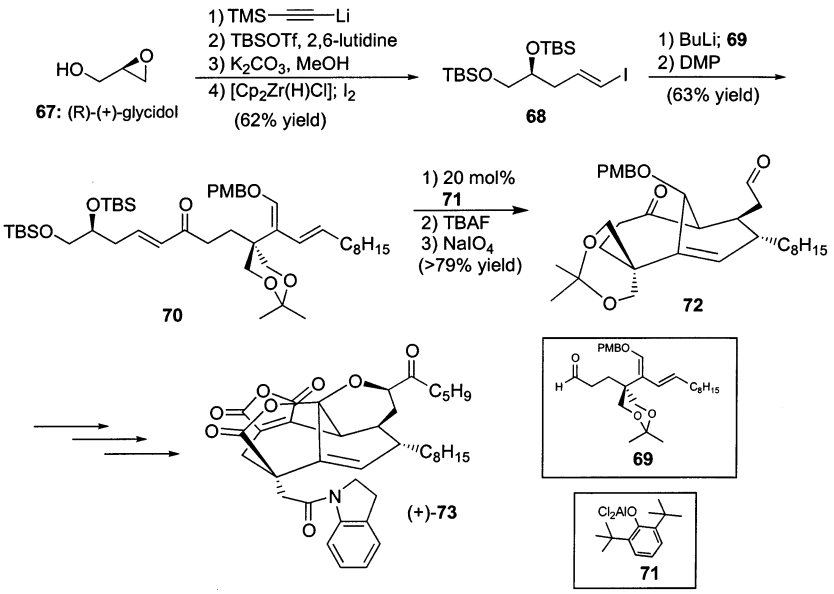


ing enol triflate, followed by carboxylation to yield an enoate. Subsequent interconversion of the dithiane protecting group to a methyl acetal using Stork's procedure gave enoate **59**. The carboxylate ester was then fully reduced and converted regioselectively into diol **60**. Completion of the anhydride function was accomplished in an ingenious one-pot sequence. This involved conversion of the primary alcohol function in **60** to a mesylate, epoxide formation, β-elimination, cyclization, tautomerization, autoxidation, and ammonia extrusion to yield maleic anhydride **61.**[64,65,68]

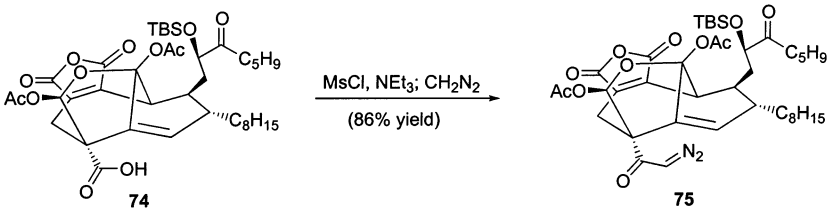
The greatest challenge remaining was to convert the locally symmetric acetonide in **61** into the quaternary γ-hydroxylactone found in the phomoidrides (Scheme 11). Thus, a series of protecting group manipulations (**61** → **62**), oxidation of the bridgehead alcohol to the corresponding ketone, acetonide removal with concurrent lactol formation, and masking of the remaining primary alcohol as its TES ether furnished hemiacetal **63**. This was then converted to aldehyde **64** and subjected to an Arndt−Eistert sequence to give rise to acid **65**. Coupling of the resulting free acid with indoline, deprotection of the TBS acetal, oxidation to the lactone, and a two-step deprotection sequence of the indoline amide gave phomoidride A (**1**). Interconversion studies elegantly illustrated that phomoidride A (**1**) could be readily cyclized to phomoidride B (**2**) using methanesulfonic acid in chloroform, while **2** could be converted back into **1** by using LiOH in a THF/water mixture.

Nicolaou and colleagues subsequently published the first asymmetric total synthesis of the phomoidrides, which established the absolute stereochemistry of the natural products.[66,69] Their approach relied upon intercepting their racemic route at intermediate aldehyde **69** (Scheme 12). They began with (*R*)-(+)-glycidol (**67**) and, in a four-step sequence involving alkylation and hydroiodination, arrived at vinyl iodide **68**. This intermediate was converted to the corresponding vinyllithium reagent, treated with aldehyde **69** (derived from racemic intermediate **53**; see Scheme 8), and oxidized to provide triene **70**. After considerable experimentation, it was found that Lewis acid **71** catalyzed the Diels−Alder reaction to produce a 5.7:1 mixture (70% d.e.) of diastereomeric cycloadducts. These were deprotected, chromatographically separated, and oxidatively cleaved with sodium periodate to provide enantiomerically enriched aldehyde **72**. This intermediate was carried through the previously published racemic synthesis to provide indoline (+)-**73**. The Nicolaou group determined the absolute configuration of the natural product by comparing **73** to the analogous indoline derived from natural phomoidride B. The synthetic compound possessed the opposite optical rotation to fungal material.

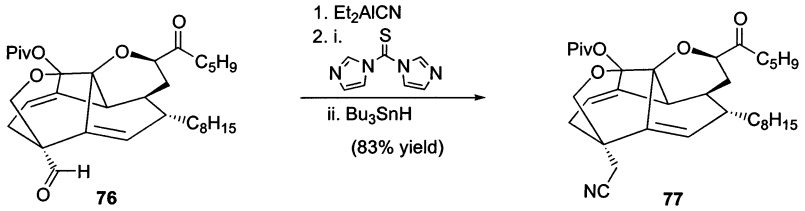
Scheme 12. Nicolaou's Asymmetric Total Synthesis



Scheme 13. Nicolaou's Acyl Mesylate Diazotization



Scheme 14. New One-Carbon Homologation Methodology

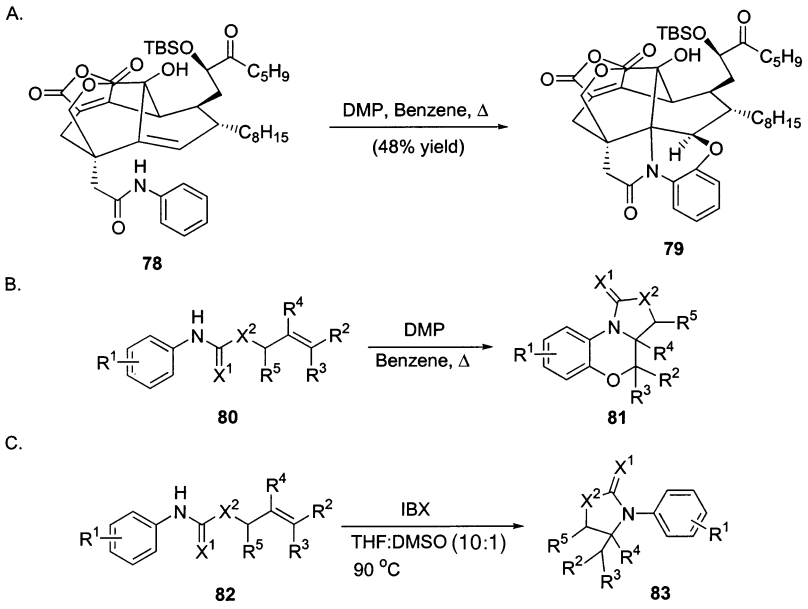


Highlight: Novel Chemistry from the Nicolaou Group's Total Synthesis. α-*Diazoketones Using Acyl Mesylates.* En route to accomplishing their racemic and asymmetric total syntheses, Nicolaou and co-workers discovered multiple novel chemical processes, which they followed up in detail. The first published of these reactions was born out of attempts to effect an Arndt−Eistert homologation of sterically hindered acid **74** (Scheme 13).[71] Because activation of this group toward the addition of diazomethane could not be effected using the acid chloride, it was reasoned that an even more reactive reagent would be necessary. Ultimately, the desired acylation with diazomethane to provide α-diazoketone **75** was accomplished through the intermediacy of an acyl mesylate. This protocol was tested on a number of hindered carboxylic acid derivatives, and it proved quite useful in providing the corresponding α-diazoketones in good to excellent yields. In this same paper, Nicolaou and co-workers were able to isolate and characterize a stable acyl mesylate. This proved the intermediacy of such a species in their reaction.

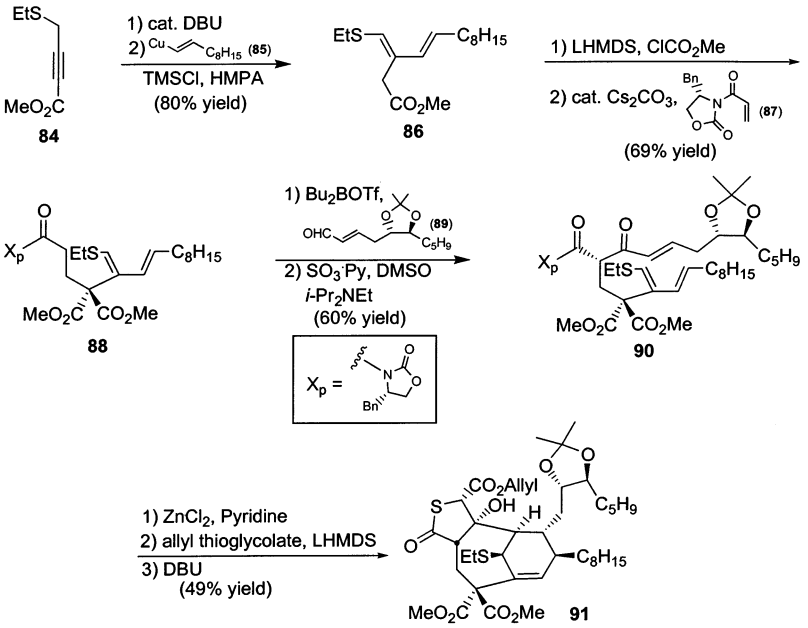
One-Carbon Homologation of Hindered Aldehydes. Later, through efforts to improve upon this one-carbon homologation, Nicolaou and co-workers developed an alternative approach employing a cyanation−deoxygenation sequence (Scheme 14).[72] Thus, addition of cyanide ion to hindered aldehyde **76** took place under mild conditions in the presence of both acid and base labile functionalities. The resulting cyanohydrin could be derivatized as its thiocarbamate and deoxygenated under radical conditions to yield homologated nitrile **77**. This reaction was extended to a range of diverse substrates and effected the desired transformation in high yields.

Novel Reactions of Iodine(V) Reagents. Another interesting and useful set of chemical transformations were discovered during Nicolaou's attempt to oxidize anilide **78** to the corresponding bis-hemiacetal.[73,76,77] In the event, it was observed that a tandem ortho aromatic oxidation, intramolecular [4+2] cycloaddition sequence had occurred, generating polycyclic morpholine derivative **79** (Scheme 15A). While it was determined that this tandem reaction was not general for all olefin-containing anilides, the method was effectively extended to anilides whose olefins were contained within ring structures (Scheme 15B). In this way, morpholine derivatives with complex

Scheme 15. Novel Hypervalent Iodine-Mediated Cyclization Reactions



Scheme 16. Fukuyama's Construction of the Bridgehead Olefin



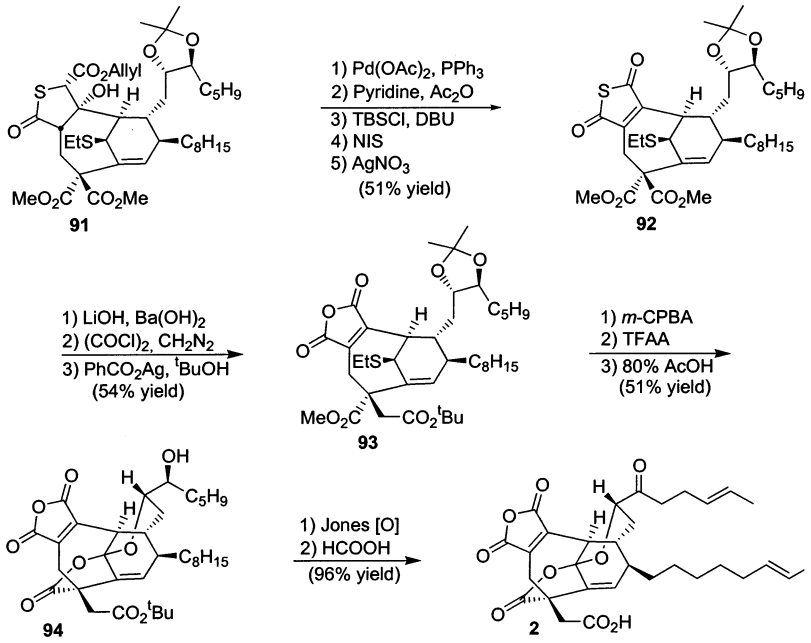
molecular architectures were generated (**80** → **81**). The proposed mechanism for this transformation involves coordination of the hypervalent iodine reagent to the anilide nitrogen with concurrent displacement of acetate, followed by oxygen transfer from iodine to carbon, and intramolecular [4+2] cycloaddition of the resulting *ortho*-quinone imide with the pendant olefin.

Interestingly, when these same substrates were treated with IBX, an entirely different reaction outcome was observed.[74,78,79] In this case, hypervalent iodine complexation with the anilide nitrogen proceeded to give a putative amidyl radical intermediate, which was capable of performing a 5-*exo*-trig radical cyclization reaction into the pendant olefin. These reactions proceeded in high yields to afford the corresponding cyclization products (Scheme 15C; **82** → **83**). The development of both the IBX and the Dess−Martin periodinane-mediated reactions opened up many other possibilities in the design of new hypervalent iodine reagents and reaction manifolds. This chemistry has been explored extensively and detailed in papers by Nicolaou and co-workers.[75,80,81]

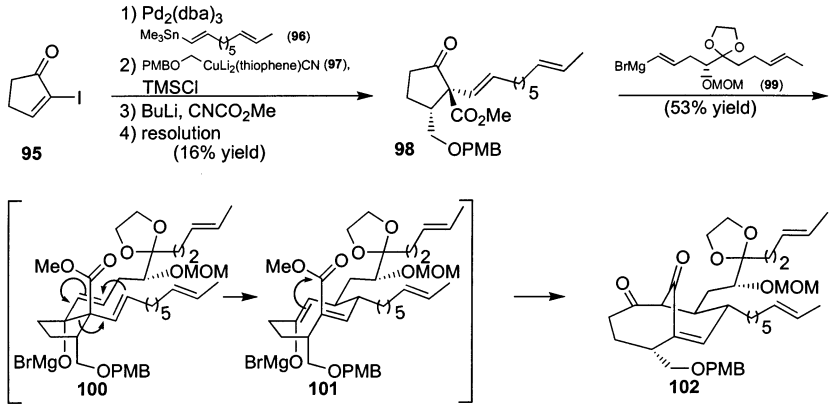
2. Tohru Fukuyama and Colleagues

Professor Tohru Fukuyama and co-workers at the University of Tokyo completed the second total synthesis of the phomoidrides, which also represented the second asymmetric route to these molecules.[82,83] Like Nicolaou, Fukuyama chose to employ a type II IMDA strategy for the construction of the phomoidrides' bicyclo[4.3.1]decene core (Scheme 16). He was then able to exploit some exquisitely chemoselective chemistry for the facile completion of the total synthesis.

Scheme 17. Completion of Fukuyama's Total Synthesis



Scheme 18. Shair's Assembly of the Carbocyclic Core



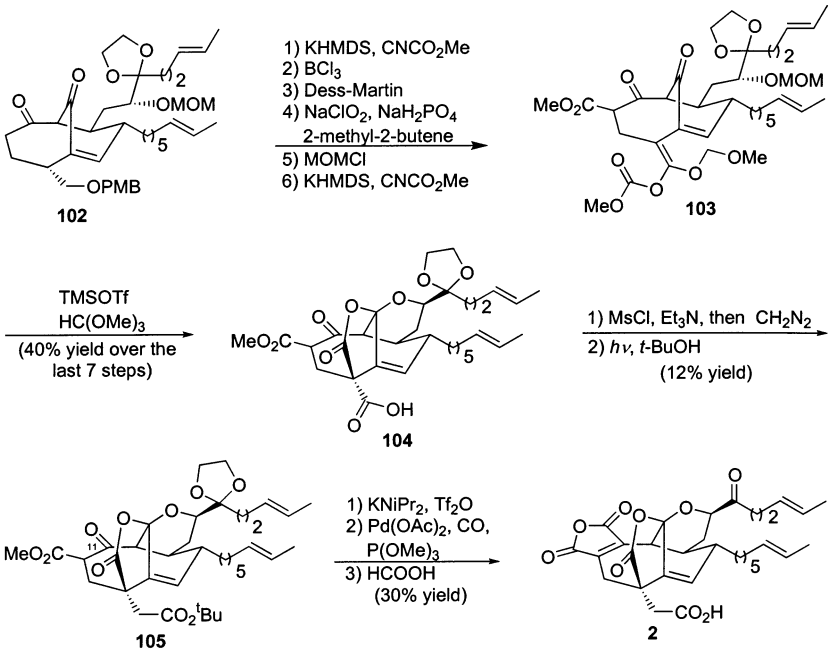
The Fukuyama group began their efforts with methyl 4-ethylthio-2-butynoate (**84**). This was treated with catalytic DBU to effect isomerization to the corresponding allene and then reacted with organocopper reagent **85** to provide 1,4-addition product **86**. Alkylation with methyl chloroformate and Michael addition of the resulting malonate into chiral acrylamide **87** gave diester **88**. Diastereoselective aldol reaction of **88** with aldehyde **89** followed by oxidation provided triene **90** in good yield, and a Diels–Alder cycloaddition catalyzed by $ZnCl_2$ furnished the desired bridgehead olefin. The chiral Evans oxazolidinone was replaced with lithium allyl thioglycolate, and an intramolecular aldol type cyclization gave γ-hydroxy thiolactone **91**.

The completion of Fukuyama's synthesis is depicted in Scheme 17. Deprotection of the allyl group in **91** followed by a one-pot dehydration and decarboxylation sequence gave a thiobutenolide. This was converted to thiomaleic anhydride **92** in three steps proceeding via the oxidation of a 2-silyloxythiophene derivative. Subsequent treatment with $LiOH/Ba(OH)_2$ gave rise both to maleic anhydride formation and to diastereoselective methyl ester saponification to yield a carboxylic acid. An Arndt–Eistert procedure then provided homologated ester **93**. Pummerer rearrangement and acetonide deprotection yielded **94**, and Jones oxidation and *tert*-butyl ester deprotection completed the total synthesis of phomoidride B (**2**).

3. Matthew D. Shair and Colleagues

The third phomoidride total synthesis to be published was accomplished by Professor Matthew Shair and co-workers at Harvard University (Scheme 18).[84,85] This route involves as its key step a "triple-domino" cyclization reaction, which proceeds in a single convergent operation to provide a highly functionalized bicyclo[4.3.1]decene core structure. Thus, synthetic efforts in the Shair group were initiated with a Stille cross-coupling reaction between 2-cyclopentenyl iodide (**95**) and stannane **96**. Conjugate addition with cuprate **97**, acylation with Mander's reagent, and kinetic resolution furnished ketone **98**, a substrate for the tandem phomoidride core-forming reaction. In the event, addition of Grignard reagent **99** to ketone **98** furnished **102** in good yield. This triple domino cyclization sequence (**98** → **102**) consists of chelation-controlled vinyl Grignard addition

Scheme 19. Completion of Shair's Total Synthesis

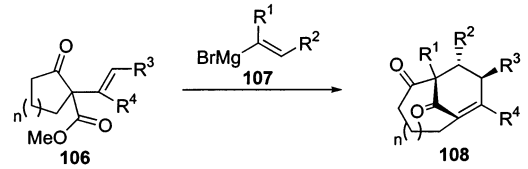


(**98** → **100**), anion-accelerated oxy-Cope rearrangement (**100** → **101**), and transannular Dieckmann-like cyclization (**101** → **102**).

Having accessed the core structure of the phomoidrides efficiently, Shair was faced with installing the C14 quaternary center and the maleic anhydride moieties to complete the total synthesis (Scheme 19). Following alkylation of **102** with Mander's reagent, the primary PMB ether was converted to enol carbonate **103** in a five-step protocol. Subjection of this compound to TMSOTf and trimethyl orthoformate gave pseudoester **104** directly. This unusual sequence is thought to involve a TMSOTf-promoted Fries-like rearrangement followed by MOM group removal and cyclization. To complete the quaternary center, Shair and co-workers employed the Arndt−Eistert homologation also utilized by Nicolaou and Fukuyama. It provided **105** in low yield, a result thought to be a function of the instability of **104**, rather than an intrinsic deficit in the Arndt−Eistert sequence in general. The total synthesis was completed by preparing the maleic anhydride moiety utilizing a Pd(0)−$P(OMe)_3$-catalyzed carbonylation reaction of the corresponding enol triflate of **105**, followed by acidification to provide phomoidride B (**2**). The use of a sterically unhindered palladium phosphite complex proved quite useful in this system given the hindered nature of the C11 enol triflate.

Highlight: Novel Chemistry Developed during Shair's Total Synthesis. At approximately the same time as the report of their total synthesis of the phomoidrides, Shair and colleagues published an exploration of their one-pot triple-domino reaction sequence (Scheme 20).[86] This cascade reaction is initiated with the alkylation of simple cyclic β-ketoesters (**106**) with vinyl Grignard reagents (**107**), and in the same pot, this is followed by anion-accelerated oxy-Cope rearrangement and transannular Dieckmann-like cyclization to afford the desired bicyclic ring systems (**108**) in excellent yields. This method

Scheme 20. Shair's Synthesis of Bridgehead Enones



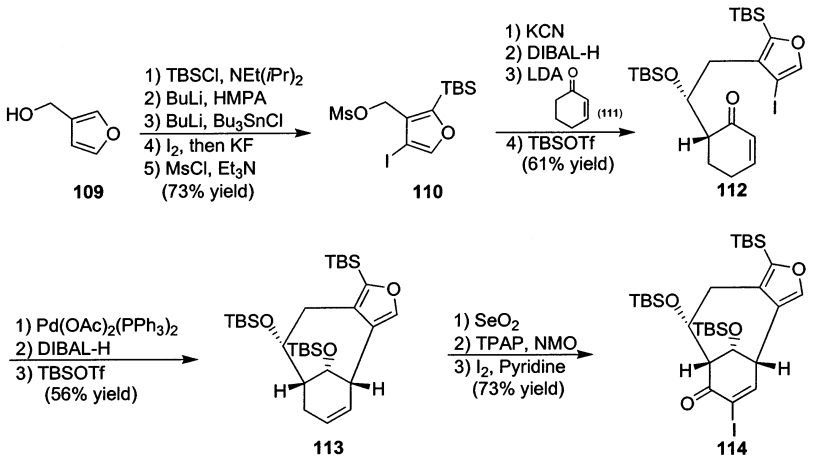
has a broad scope and allows for the inclusion of cyclic Grignard reagents, β-ketoesters containing cyclic olefins, and, ultimately, combinations of the two to provide complex tetracyclic triple domino reaction products in high yields and diastereoselectivities. Additionally, expanding the ring size of the electrophilic β-keto ester component allows for the synthesis of [5.3.1] bicyclic bridgehead olefin containing systems, including the taxane skeleton.

4. Samuel J. Danishefsky and Colleagues

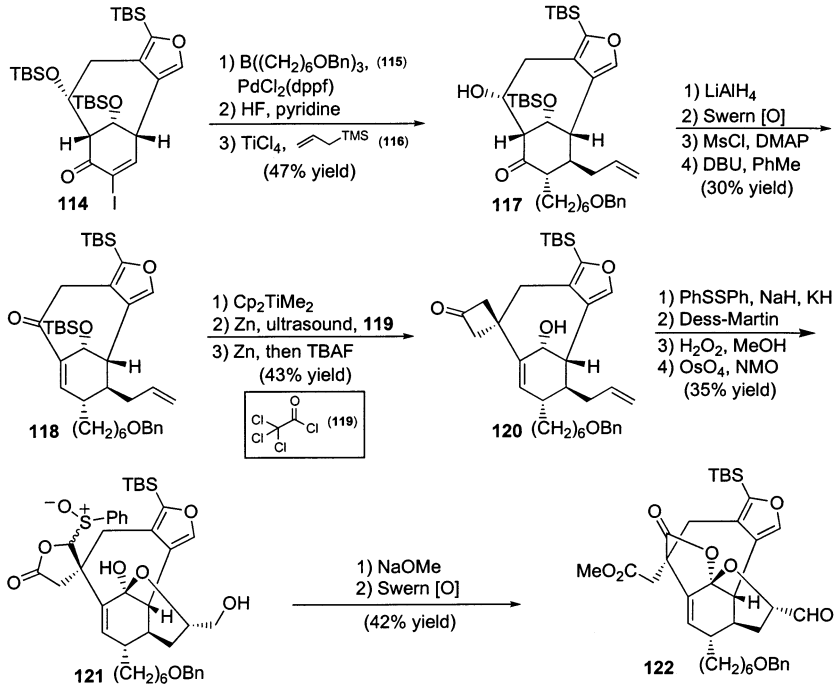
The most recently completed total synthesis of the phomoidrides is that of Professor Samuel Danishefsky and co-workers at the Sloan-Kettering Institute for Cancer Research.[12,87−90] Key aspects of this effort include a sequential aldol reaction−intramolecular Heck ring closure sequence, a diastereoselective sulfur-mediated cleavage of a spirocyclobutanone, and a late stage C7 epimerization strategy to provide phomoidrides A and B. Danishefsky's route also provides an investigation of the stabilities of natural and unnatural C7 phomoidride epimers that led to the identification of the C7-*R* epimer of phomoidride B (phomoidrides D, **4**) in fermentation broths.

The total synthesis commenced with the five-step conversion of 3-furanmethanol (**109**) to mesylate **110**. This compound was then homologated with cyanide ion, converted to the requisite aldehyde, and reacted with the lithium enolate of cyclohexenone (**111**) to give Heck ring closure substrate **112** after TBS protection (Scheme 21).

Scheme 21. Assembly of the Carbocyclic Core of the Phomoidrides



Scheme 22. Introduction of the Side Chains and the Quaternary Center

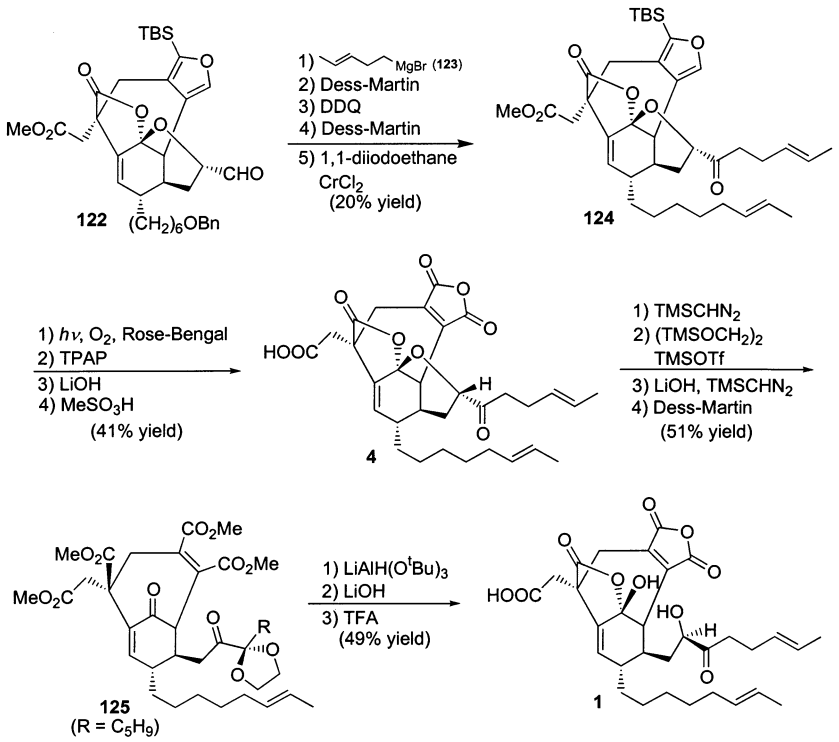


The intramolecular Heck vinylation reaction proceeded smoothly to yield tricycle **113** after reduction and TBS protection. Allylic oxidation and iodination yielded vinyl iodide **114**, an intermediate poised for the incorporation of the alkyl side chains (Scheme 22). These were installed employing first a B-alkyl Suzuki−Miyaura cross-coupling reaction[91] between **114** and trialkylborane **115** and then a Sakurai type allylation with **116**. This sequence provided the desired trans side chain stereochemistry found in the natural product. After a series of chemoselective oxidation state manipulations, the bridgehead olefin was installed via a β-elimination of a secondary mesylate to give **118**.

To incorporate the succinic acid-derived quaternary center, Danishefsky employed a unique approach. He began with Tebbe olefination of **118**, and affected on the resulting product a chemoselective [2+2] cycloaddition with dichloroketene generated from acid chloride **119**. Dechlorination with zinc yielded spirocyclobutanone **120**, and regioselective sulfenylation of **120** was then achieved using diphenyl disulfide. The molecule was then exhaustively oxidized starting with Dess−Martin oxidation of the secondary alcohol, and followed by regioselective Baeyer−Villiger oxidation of the cyclobutanone, conversion of the phenylsulfenyl lactone to the corresponding sulfoxide, and dihydroxylation of the allyl group to provide **121**. Saponification and oxidation gave lactone **122**, which has the quaternary center in place. This method for generating the quaternary center is quite distinct from methods employed by other groups.

Danishefsky's completion of the phomoidrides is detailed in Scheme 23. First, the two side chains were installed. The C1−C5 portion was incorporated via addition of Grignard reagent **123** to aldehyde **122**, and the C18−C25 piece was elaborated via debenzylation, oxidation, and reductive olefination with diiodoethane and $CrCl_2$ to give **124**. Unmasking of the anhydride was accomplished in a straightforward fashion on treatment of **124** with singlet oxygen followed by TPAP oxidation. Subsequent hydrolysis

Scheme 23. Completion of the Total Synthesis



and acidification afforded *epi*-phomoidride **4** (phomoidride D). Because at the time the Danishefsky group was targeting **1** and **2** for synthesis, they extensively explored the use of early intermediates to arrive directly at compounds with the desired C7 stereochemistry without employing epimerization protocols. They met with limited success. Ultimately, they converted phomoidride D (**4**) to **1** in a seven-step sequence, and thus completed their total synthesis.

C. Comparison of the Synthetic Routes

The multiplicity of synthetic obstacles posed by phomoidrides A and B can be divided into four main structural challenges. These are the carbocyclic core including the C15−C16 bridgehead olefin, the maleic anhydride moiety, the γ-hydroxy lactone containing the quaternary center at C14, and the stereocenter at C7. The following sections (II.C.1 through II.C.4) will highlight and compare the four total syntheses in the context of these difficult structural elements.

1. Carbocyclic Core and Bridgehead Olefin

In all four published total syntheses of the phomoidrides, the construction of the bridgehead olefin-containing carbocyclic core is undertaken at an early stage of the synthesis. On the surface, it is notable that all investigators felt that this functionality would survive later stage synthetic transformations despite the predicted tendency of strained olefins to exhibit enhanced reactivity profiles (see II.A above). Given the inherent unpredictability of endeavors in total synthesis, it was indeed fortuitous that these routes were accomplished with little interference from reaction with the double bond.

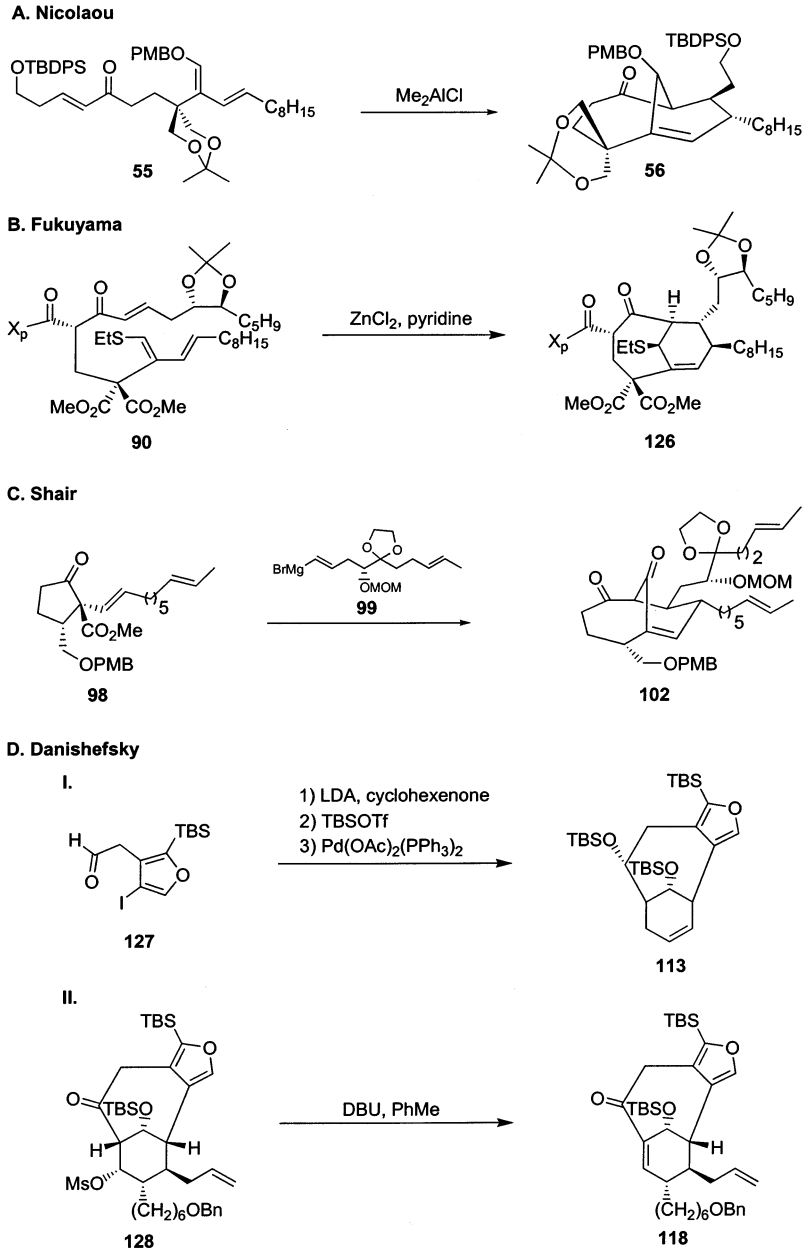
To attack the problem of the carbocyclic core, both Nicolaou (Scheme 24A; **55** → **56**) and Fukuyama (Scheme 24B; **90** → **126**) opted for a type II IMDA strategy. In both cases, this approach has the benefit of installing the bridgehead olefin concurrent with generating the carbocyclic core, positioning the pendant functionalities (such as progenitors for the olefinic side chains) with the correct relative stereochemical relationships, and allowing for the introduction of substrate-controlled asymmetry into the synthesis.

In Nicolaou's racemic synthesis, the IMDA reaction proceeds from a substrate entirely lacking chirality to generate the core structure in a stereocontrolled fashion. This represents a distinct benefit in terms of synthetic economy; four stereocenters and two ring systems are assembled in a single transformation. Fukuyama engages a similar benefit from his Diels−Alder. Also, in contrast to what might be expected for such an efficient reaction, very little price is paid in terms of substrate accessibility. A noteworthy advantage of the Fukuyama approach is the presence of a C12 carboxylate function, which controls the absolute stereochemical outcome of the IMDA reaction and can later be elaborated into the maleic anhydride moiety. This additional functionality incorporated early obviates the need to homologate the C11 or C12 centers later.

In his asymmetric synthesis (Scheme 12), Nicolaou constructs a Diels−Alder substrate elongated by one carbon, which generates chirality and directs the reaction. While this creates the need for cleavage of this extra carbon−carbon bond after the cycloaddition, the overall efficiency in accessing known intermediate **72** is not compromised.

Shair's triple-domino reaction cascade (Scheme 24C; **98** → **102**) has many of the advantages of the Nicolaou and Fukuyama Diels−Alder approaches. These include the stereocontrolled formation of the carbocyclic core, the installation of the bridgehead

Scheme 24. Syntheses of the Carbocyclic Core and Bridgehead Olefin



olefin, and, of course, the elegance of a novel, tandem chemical transformation. Asymmetry is incorporated via inclusion of an *R*-glyceraldehyde acetonide-derived vinyl Grignard reagent and a substituted cyclopentanone made enantiopure via a CBS resolution. While the reaction product lacks much of the functionality necessary for the completion of the synthesis, Shair compensates admirably for this later in the route (see Scheme 19 and discussion below).

Unlike the previous three approaches involving pericyclic reactions, the Danishefsky group assembles the core structure of the phomoidrides using a sequential aldol-Heck strategy (Scheme 24D, I; **127** → **113**). Here, substrates for the aldol-Heck cascade are accessed quickly and in high yield. However, they lack critical functionality, notably the olefin-containing side chains. These must be added after the core is formed because, in pilot studies, investigators observed a problematic oxidation of the C20 side chain during a critical allylic oxidation reaction.[89] Ultimately, to form the C15−C16 double bond, Danishefsky employs a strategy in which a mesylate group is eliminated from a bicyclo[4.3.1]-ketone to generate the corresponding conjugated enone (Scheme 23D, II; **128** → **118**). The clever incorporation of a ketone functionality in **128** controls the regiochemistry of this elimination reaction to generate the C15−C16 double bond as an enone.

2. Maleic Anhydride Moiety

The incorporation of the maleic anhydride moiety proved in many cases to be the most challenging aspect of the total synthesis. One reason for this is the steric hindrance in the vicinity of carbons 11 and 12. This peculiar property of the phomoidride core skeleton makes the elaboration of the maleic anhydride particularly difficult when either of these two carbons is functionalized. It is for this reason perhaps that three of the four approaches (Nicolaou, Danishefsky, and Fukuyama) rely upon oxidation of furan

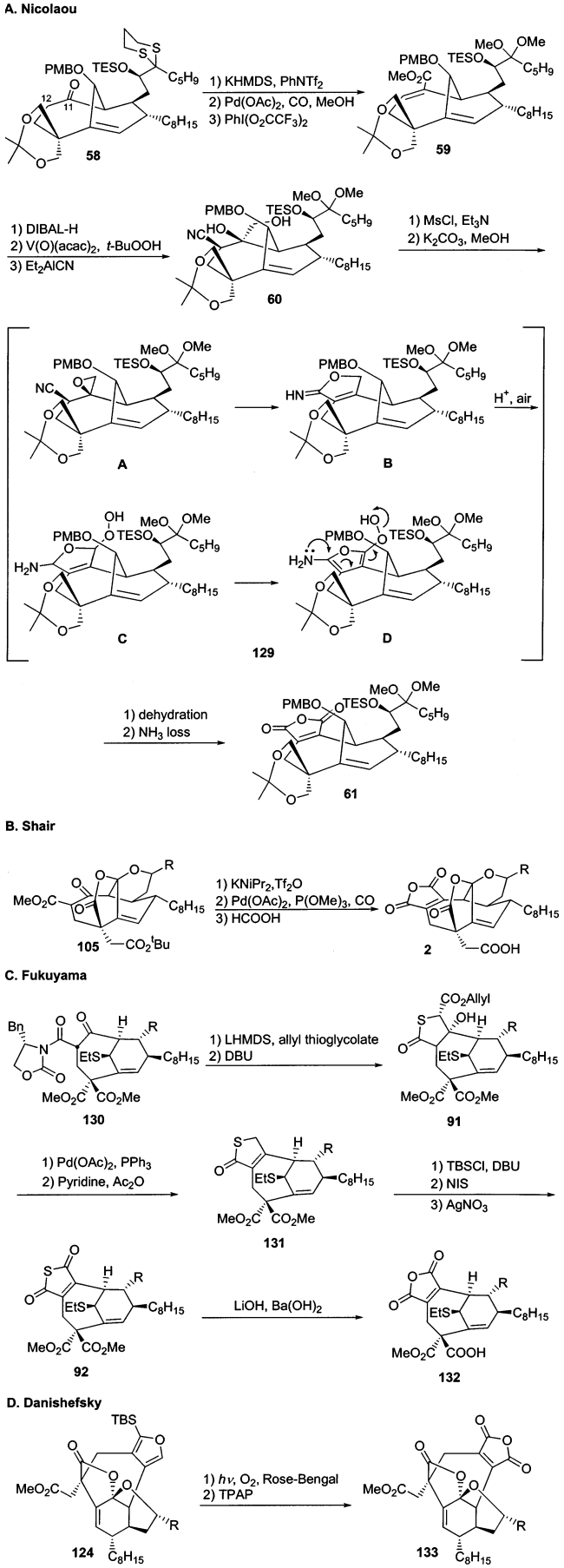
derivatives to provide the maleic anhydride; oxidants such as molecular oxygen are sterically undemanding and can easily make the necessary approach, even in a crowded environment.

As depicted in Scheme 25A, Nicolaou begins his anhydride synthesis with ketone **58** shortly after accomplishing the key Diels−Alder cycloaddition. While he might have incorporated a one-carbon unit at C12 into his Diels−Alder substrate like Fukuyama (indeed, early studies focused on the functionalization of C11 in the presence of a substituted C12), efforts to advance these intermediates failed, likely due to severe steric shielding. After a great deal of effort, Nicolaou arrives at an unusual and elegant route for the conversion of Diels−Alder adduct **58** into the elusive maleic anhydride. This sequence begins with a triflation−carbonylation protocol initiated at the C11 ketone to yield enone **59**. This compound is epoxidized chemoselectively at the electron poor C11−C12 olefin and made to undergo a surprising syn epoxide opening with Et_2AlCN to provide cyanodiol **60**. The subsequent conversion to the maleic anhydride takes place in a single pot and involves a succession of interesting chemical transformations. It proceeds as follows: compound **60** is mesylated at its primary hydroxyl, and the resulting intermediate is converted with base to a C11 spiroepoxide (**129A**). This readily undergoes base-induced β-elimination and spontaneous 5-*exo*-dig hydroxyl cyclization into the adjacent nitrile to provide **129B**. While it was initially predicted that imino butenolides such as **129B** would be too unstable to characterize, the Nicolaou group was able to confirm its intermediacy using model substrates. Finally, it is postulated that acid-mediated tautomerization of **129B** leads to an aminofuran, and autoxidation of this transient intermediate with atmospheric oxygen provides hydroperoxide **129C**. Further tautomerization of **129C** to **129D**, followed by dehydration and loss of ammonia, gives rise to the desired maleic anhydride (**61**). An initially unforeseen benefit of this approach is that it provides maleimide and hydroxyamide byproducts, which can be converted into phomoidride analogues.[68,69]

The Shair group's synthesis of the maleic anhydride stands alone among the four routes in that it does not involve the oxidation of a furan type structure (Scheme 25B). However, like the Nicolaou group, the Shair group must contend with the difficulties attending the functionalization of C11 in an intermediate substituted at C12. Also, as with the Nicolaou group's approach, the obstacle proved fruitful; a carbonylation procedure was developed involving the exposure of the enol triflate of **105** to palladium acetate and trimethyl phosphite under an atmosphere of carbon monoxide. The need to employ this phosphite as a ligand for palladium is thought to arise from its small cone angle, which allows the metal complex access to the hindered C11 enol triflate.

Like Nicolaou, Fukuyama (Scheme 25C) and Danishefsky (Scheme 25D) both oxidize furan derivatives to access the maleic anhydride. Fukuyama utilizes an intramolecular alkylation−decarboxylative elimi-

Scheme 25. Syntheses of the Maleic Anhydride



nation sequence (**130** → **131**) to reach a thiobutenolide (**131**). This is converted to a silyloxythiophene, oxidized to the corresponding thiomaleic anhydride (**131** → **92**), and converted hydrolytically into the desired functional group (**92** → **132**). Danishefsky, whose route incorporates a silylfuran from the beginning, is able to form the maleic anhydride concisely via singlet oxygen oxidation (**124** → **133**). Here, Fukuyama's rapid access to the phomoidride core structure leads him to sacrifice some expediency in making the maleic anhydride, while Danishefsky's incorporation of the silylfuran moiety at the outset allows rapid unmasking of this functional group.

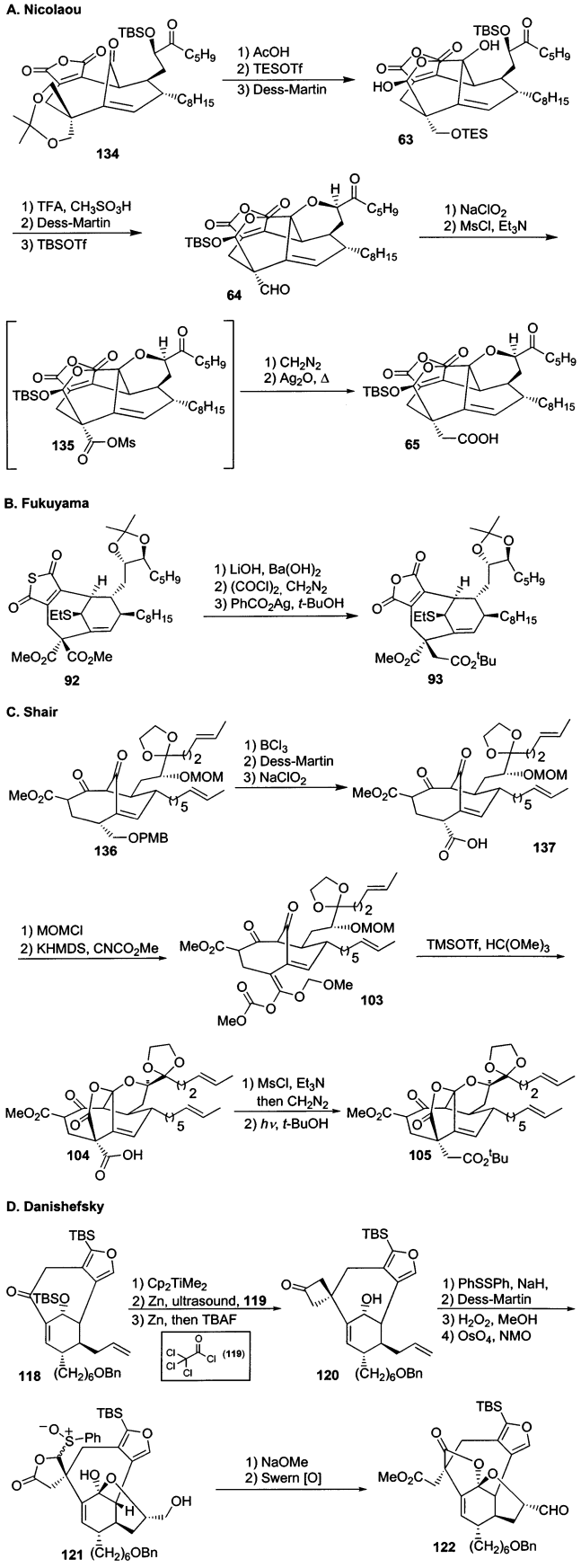
3. C14 Quaternary Center

Synthesis of the C14 quaternary center presented a great obstacle to synthetic efforts because of its asymmetry. Two carbons, C28 and C29, are situated on one diastereotopic face of C14, and C27 lies on the other held in a γ-hydroxy lactone or pseudoacid function (see Figure 1). Innovative methods were therefore developed by all four researchers in order to conquer this challenge.

Nicolaou (Scheme 26A) and Fukuyama (Scheme 26B) both rely on the bicyclo[4.3.1] skeleton to direct reactions to one face of a diastereotopic C14 center. This approach has the advantage of allowing economic access to a Diels−Alder substrate; however, in both cases, this simplification necessitates a chemoselective one-carbon homologation to form the C28−C29 side chain. During the process of his synthetic endeavors, Nicolaou expends a great deal of experimental effort arriving at an appropriate substrate for this transformation and settles on the route depicted in Scheme 26A.[69] He finds that only when C27 is held in a silyl acetal (e.g., in **64**) and C7 is internally protected as its pyran in the Arndt−Eistert homologation (**64** → **65**) is subsequent completion of the total synthesis viable. Unfortunately, this sequence is found to be low yielding, a problem that he attributes to the presence of the unstable anhydride moiety.[69] Fukuyama obtains a slightly higher yield in his homologation sequence. Differentiation between the geminal diesters at C14 takes place in the same pot as the final step of the maleic anhydride formation, and a similar Arndt−Eistert approach as that employed by Nicolaou provides the fully elongated C28−C29 chain (**92** → **93**).

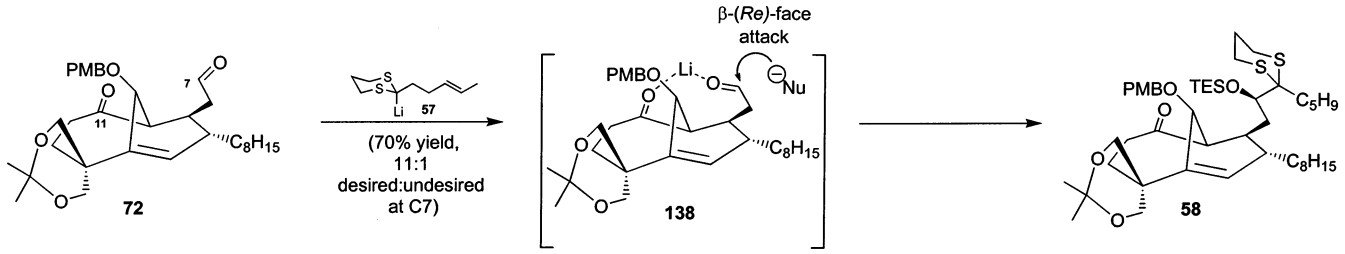
Shair (Scheme 26C) also utilizes an Arndt−Eistert homologation as a key step in forming the quaternary center but arrives at his substrate differently from the two previous groups. Instead of desymmetrizing a prochiral quaternary center, he employs a diastereoselective acyl transfer reaction of an enol carbonate (**103**). Unfortunately, this gives rise to a substrate that undergoes the homologation reaction in a low yield over two steps (**104** → **105**). Shair points out in his paper that this disappointing yield was more a function of the sensitivity of substrate **104** (Scheme 19) than a deficiency inherent to the Arndt−Eistert approach. Furthermore, a similar compound[68] was reported by Nicolaou to be unstable under homologation conditions, likely due to its tendency to undergo decarboxylation.

Scheme 26. Syntheses of the Quaternary Center

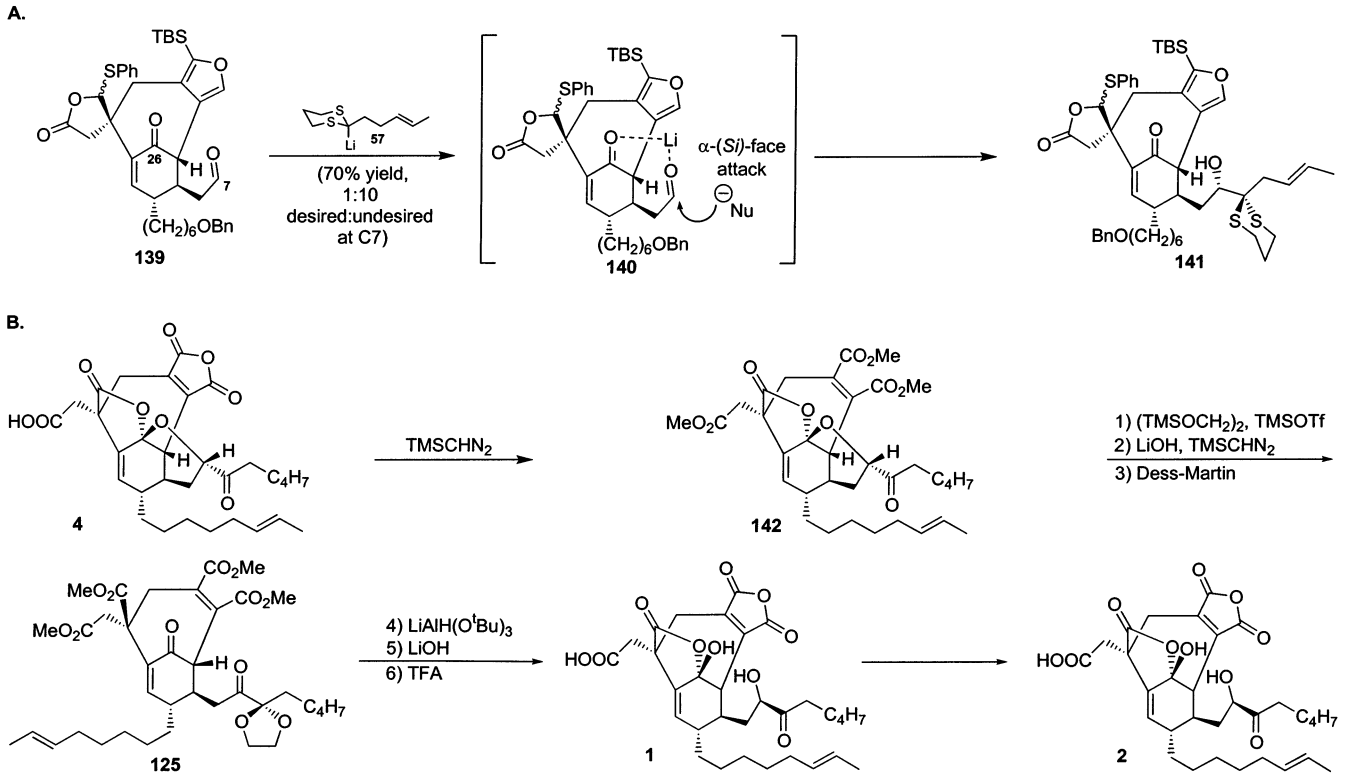


Like Nicolaou and Fukuyama, Danishefsky (Scheme 26D) utilizes a locally symmetric intermediate, spirocyclobutanone **120**, which must be desymmetrized.

Scheme 27. Nicolaou's C7 Alkylation



Scheme 28. Danishefsky's Construction of the C7 Stereocenter



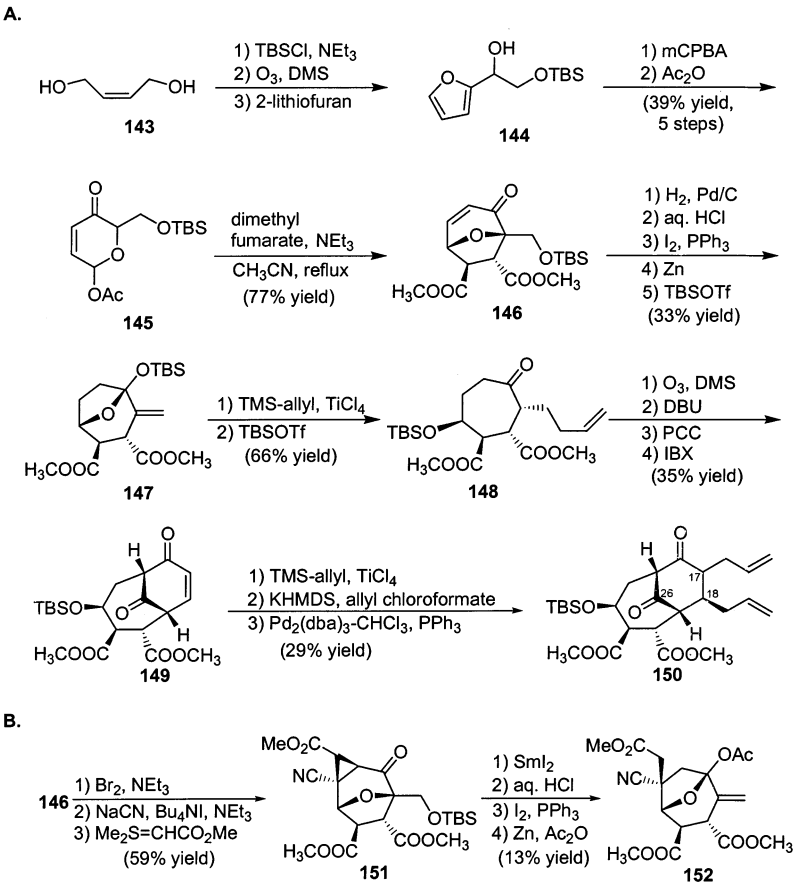
However, unlike the other three total syntheses, this route does not require Arndt−Eistert homologation steps. He achieves this feat by using a very unusual substrate-directed sulfenylation Baeyer−Villager oxidation sequence, which leads to the formation of the desired quaternary center in sulfoxide **121**. This compound is saponified and oxidized to provide the desired pseudoester **122**. It is worth observing that the dichloroketene cycloaddition and Baeyer−Villiger steps take place chemoselectively in the presence of an allyl group and the bridgehead olefin.

4. C7 Stereocenter

Unlike Fukuyama and Shair, who bring in the required stereochemistry at C7 from chiral starting materials (see Schemes 16 and 18), both Nicolaou (Scheme 27) and Danishefsky (Scheme 28) generate this stereocenter using diastereoselective alkylation reactions of aldehydes.[92] In Nicolaou's case, the installation of this stereochemistry proves relatively unproblematic; initial alkylation attempts on ketone **72** provided the desired stereochemistry in an 11:1 ratio. Nicolaou cites the presence of the C11 ketone as the controlling factor in this addition reaction.[69] It is reasoned that the lithium counterion of the dithiane-derived nucleophile coordinates both the C7 aldehyde and the C11 ketone providing a sort of chelation control in which the nucleophile attacks the less hindered β-face of the aldehyde (see **138**, Scheme 27). Experiments to test this hypothesis were performed in which this ketone was replaced with ester, protected hydroxymethyl, and hydroxymethyl functionalities. Consistent with the proposed mechanism, the diastereoselectivity of the alkylation was reversed with the ketone absent.[69]

Danishefsky had no such luck in his late stage alkylation of aldehyde **139**. Treating this compound with lithiated dithiane **57** led to the undesired diastereomer in a 1:10 ratio (Scheme 28A). Here, instead of achieving lithium counterion chelation control with a ketone at C11 (where Danishefsky has his silyl furan in place), Danishefsky postulates that an unfavorable "lithio channel" between the ketones at C26 and C7 (**140**) might be controlling the stereochemical outcome in the conversion to **141**. He therefore reduces the C26 ketone, and while he achieves higher levels of the desired stereoisomer from alkylation of this compound, these are not

Scheme 29. Ohmori's Approach to the Phomoidrides



deemed useful for completion of the total synthesis. He opts instead to return to an intermediate derived from his initial osmylation approach (**4**; Scheme 28B) for a seven step sequence (**4** → **1**), which converts *epi*-phomoidride B (phomoidride C, **4**) to phomoidride B (**2**).[90] This epimerization involves the oxidation of a C7 hydroxyl to its ketone (**125**), followed by a hydride reduction to give a separable mixture of diastereomers in a 1:1 ratio. It is worth pointing out that the detour followed by Danishefsky toward compounds epimeric at C7 paved the way for the discovery of natural phomoidrides epimeric at C7.[12] These were later isolated from primary fungal cultures by the Sulikowski group and named phomoidrides C and D.[13]

D. Synthetic Approaches toward the Phomoidrides

In addition to the four completed total syntheses, 18 research groups have published synthetic approaches toward the phomoidrides. These have allowed access to intermediates of wide-ranging complexity, and some will undoubtedly lead to completed synthetic routes. Below are summarized the published routes organized according to key disconnection.

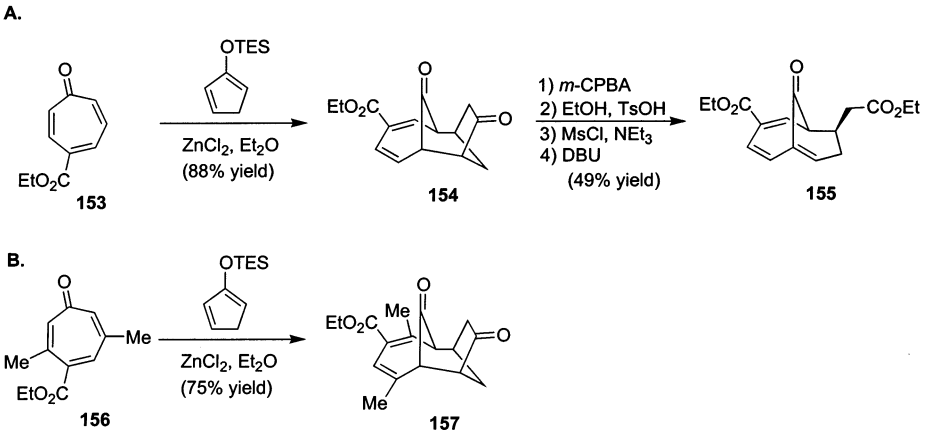
1. Routes That Involve Cycloadditions To Form the Core

Since the time of the Nicolaou and Fukuyama groups' first published reports of their type II IMDA approaches, two other laboratories have detailed routes toward the phomoidride core that involve cycloaddition strategies. These include contributions from Naoki Ohmori and colleagues at Hiroshima University and James L. Gleason and colleagues at McGill University.

Naoki Ohmori and Colleagues. Ohmori and coworkers have applied an intermolecular [5+2] cycloaddition strategy between a transient oxidopyrylium intermediate and dimethyl fumarate (Scheme 29A) in their approach to the phomoidrides.[93−95] The synthesis began with a simple five-step conversion of (*Z*)-but-2-ene-1,4-diol (**143**) to oxidopyrylium precursor **145** by way of furan **144**. Intermolecular [5+2] cycloaddition between **145** and dimethyl fumarate proceeded readily to provide oxabicyclo[3.2.1]octene derivative **146**. This was then transformed via a reductive ring opening reaction into exocyclic olefin **147**. Lewis acid-catalyzed allylation and TBS protection provided **148**, which was subjected to ozonolysis, transannular aldol reaction, and exhaustive oxidation to yield bicycle **149**. Conjugate allylation, and further allylation using palladium and allyl chloroformate, furnished advanced intermediate **150**. This contains a vicinal diester for elaboration to the maleic anhydride and the appropriate stereochemical relationship between the C18 side chain and the C26 bridge carbon. While **150** was obtained as a single stereoisomer, the relative stereochemistry between the C17 and the C18 allyl groups was not determined.

Efforts toward the installation of the quaternary center are also described. Here, **146** was first elaborated in three steps to nitrile **151**. Then, reductive

Scheme 30. Gleason's Route to the Phomoidride Core



cyclopropane ring opening with samarium diiodide, followed by a similar sequence to that used previously (**146** → **147**), provided advanced intermediate **152**. This compound contains functionality appropriate for advancement to the natural phomoidrides (Scheme 29B). It seems reasonable that the bridgehead double bond, C14 quaternary center, maleic anhydride, and olefin-containing side chains are all within the reach of this approach.

James L. Gleason and Colleagues. Gleason's initial approach[96] (Scheme 30A) began with the zinc chloride-catalyzed [6+4] cycloaddition of readily available tropone **153** with 2-triethylsilyloxycyclopentadiene. This reaction provided cycloadduct **154** with high regio- and diastereoselectivity. Regioselective Baeyer−Villiger oxidation followed by ethanolic lactone opening, mesylate formation, and elimination yielded bridgehead olefin **155**. The results of a cycloaddition with a more elaborately functionalized tropone substrate (**156** → **157**; Scheme 30B) are also provided. Using this approach, one can imagine appending the quaternary center and maleic anhydride portions of the phomoidrides.

2. Routes Based upon Sigmatropic Rearrangements

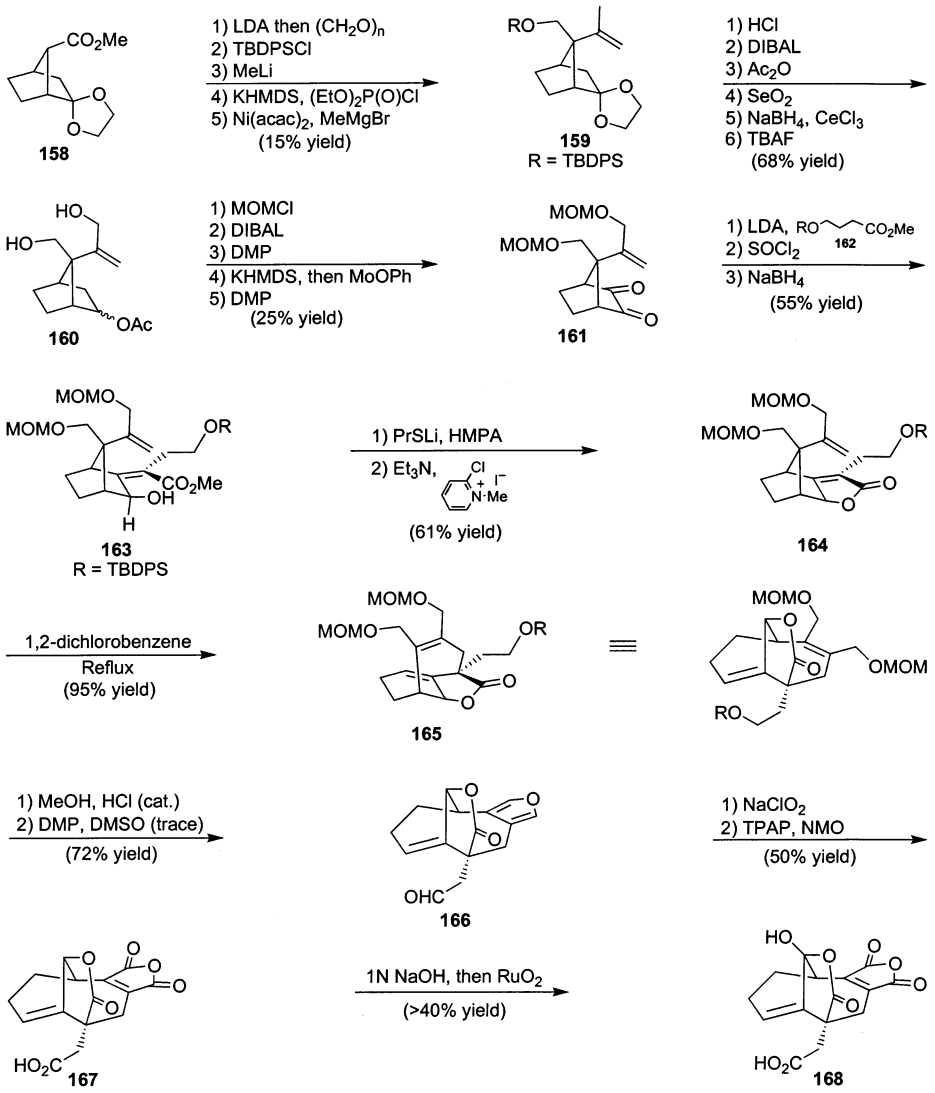
A commonly employed disconnection of the phomoidride core structure involves the use of sigmatropic rearrangements, specifically, variants of the Cope rearrangement. For example, as detailed above, Shair and co-workers[85] employed an anion-accelerated oxy-Cope rearrangement in tandem with a transannular Dieckmann type cyclization to complete his total synthesis. Utilizing disconnections distinct from Shair's, the laboratories of Professor Derrick L. J. Clive at the University of Alberta and those of Professor James L. Leighton at Columbia University both pursued oxy-Cope and thermal Cope rearrangement strategies in the context of their synthetic efforts. These strategies, along with contributions from Martin G. Banwell at The Australian National University, Huw M. L. Davies at the State University of New York at Buffalo, and Kyriacos C. Nicolaou at the Scripps Research Institute, are summarized below.

Derrick L. J. Clive and Colleagues. Clive and collaborators have worked extensively on an oxy-Cope rearrangement strategy toward the carbocyclic core of the phomoidrides. In his initial synthetic approach to these natural products, Clive performed simplified model studies utilizing an anionic oxy-Cope protocol to assemble the carbocyclic core structure of the phomoidrides.[97] This reaction proceeded only under very harsh conditions and did not tolerate functionality necessary for advancement of the model studies. Eventually, a relatively mild procedure employing a silyloxy-Cope reaction was developed to allow for the synthesis of more highly elaborated systems.[98−101] Their most advanced approach[102] (Scheme 31) involves the use of a strain-assisted Cope rearrangement to provide the fully elaborated carbocyclic core of the phomoidrides lacking only the olefinic side chains.

The approach commenced with ester acetal **158**, easily derived through literature protocols from norbornene. Formation of the ester enolate of **158**, trapping with paraformaldehyde, and silyl protection gave a β-silyloxy ester. This was converted to the corresponding methyl ketone and homologated to isopropene **159** using a Nickel-mediated Kumada type coupling approach on an intermediate enol phosphate. Conversion of the acetal in **159** to a diastereomeric mixture of acetates, followed by allylic oxidation, reduction, and silyl deprotection, provided diol **160**. This diol was protected as the corresponding bis-methoxymethyl ethers, subjected to acetate removal, and converted in three steps to vicinal diketone **161**. Condensation with γ-silyloxy methyl ester **162**, followed by dehydration and diastereoselective reduction, gave methyl ester **163**. This then underwent ester deprotection and lactonization to yield strained butenolide **164**.

On heating in 1,2-dichlorobenzene, **164** readily underwent thermal Cope rearrangement to provide bridgehead olefin **165**. The methoxymethyl and silyl ethers in **165** were cleaved with acid, and the resulting triol was converted to a furan aldehyde (**166**). Subsequent sodium chlorite oxidation achieved simultaneous conversion of the aldehyde to the corresponding acid and the unexpected oxidation of the furan to a regioisomeric mixture of hydroxy butenolides. These could both be converted to anhydride **167** upon perruthenate oxidation (TPAP/NMO). Finally, installation of the C26 hemiacetal was accomplished on treatment with basic ruthenium di-

Scheme 31. Clive's Synthesis of the Phomoidride Core



oxide to yield Clive's most advanced intermediate **168**. This compound contains all of the component functionality of the phomoidride carbocyclic core with the exception of the alkyl side chains.

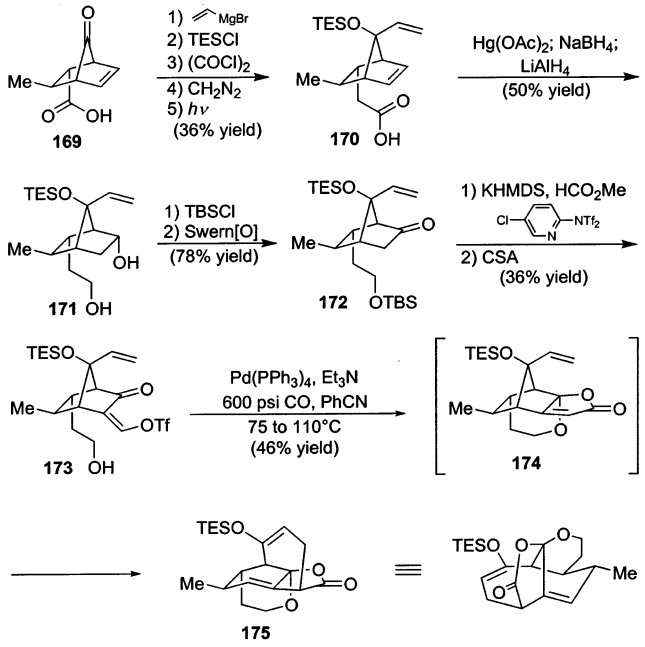
James Leighton and Colleagues. The Leighton group has capitalized on a silyloxy-Cope rearrangement approach in their studies toward the phomoidrides.[103,104] Importantly, they were the first group to incorporate a butenolide into a Cope substrate (e.g., **174**) in order to increase ring strain in the tricyclic skeleton and facilitate desired rearrangement.[103] This approach goes one step further in forming the butenolide and performing the rearrangement as a one-pot tandem process via the homologation of an enol triflate (Scheme 32). The most advanced approach (Scheme 33)[104,105] gives rise to a single silyloxy-Cope product from a mixture of enol triflate olefin isomers and incorporates the C14 quaternary center.

The synthesis began with known acid **169** (prepared in four steps from methyl crotonate). Vinylation at the 7-position and an Arndt−Eistert sequence furnished diene **170**. Chemo- and regioselective oxymercuration, followed by reduction, gave diol **171**, which was then protected and oxidized to provide ketone **172**. Formation of **173**, the silyl-deprotected enol-triflate of **172**, set the stage for a one-pot carbonylation, butenolide formation, silyloxy-Cope rearrangement sequence to furnish **175**.

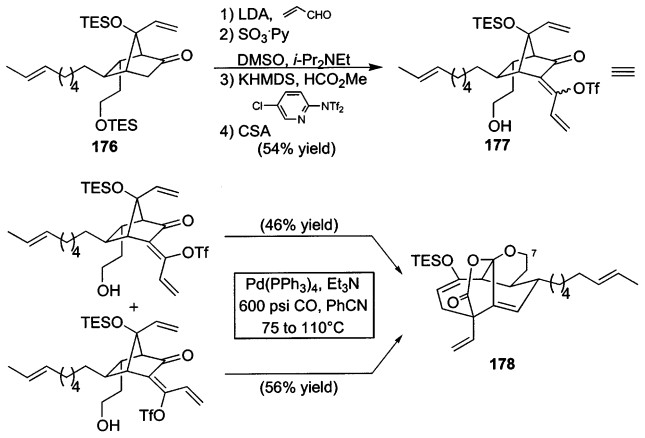
To address the formation of the quaternary center and, eventually, the maleic anhydride portions of the molecule, Leighton has pursued routes toward more highly functionalized intermediates. These efforts are depicted in Scheme 33. This route began with the condensation of ketone **176** (prepared in 11 steps from commercially available starting materials), with acrolein, followed by oxidation, mono TES-deprotection, and conversion to enol-triflates **177**. Employing the previously described carbonylation conditions, Leighton demonstrated that both regioisomeric enol triflates could undergo the cascade reaction sequence to produce **178**. To complete the synthesis, Leighton faces the same challenge as did Nicolaou and Shair: to convert the C11 TES enol ether into the maleic anhydride unit found in the phomoidrides.

Martin G. Banwell and Colleagues. Banwell and co-workers at The Australian National University have chosen a different anionic oxy-Cope variant for their studies with the phomoidrides (Scheme 34).[106] Here, in a sequence reminiscent of earlier work from this laboratory toward the taxol skeleton,[107] the

Scheme 32. Leighton's Construction of the Phomoidride Core



Scheme 33. Carbonylation-Initiated Cascade To Make the Quaternary Center



sigmatropic rearrangement is performed on a bicyclo[2.2.2]octane skeleton. It is then followed by a Wolff ring contraction affording the bicyclo[4.3.1]decene core found in the natural products.

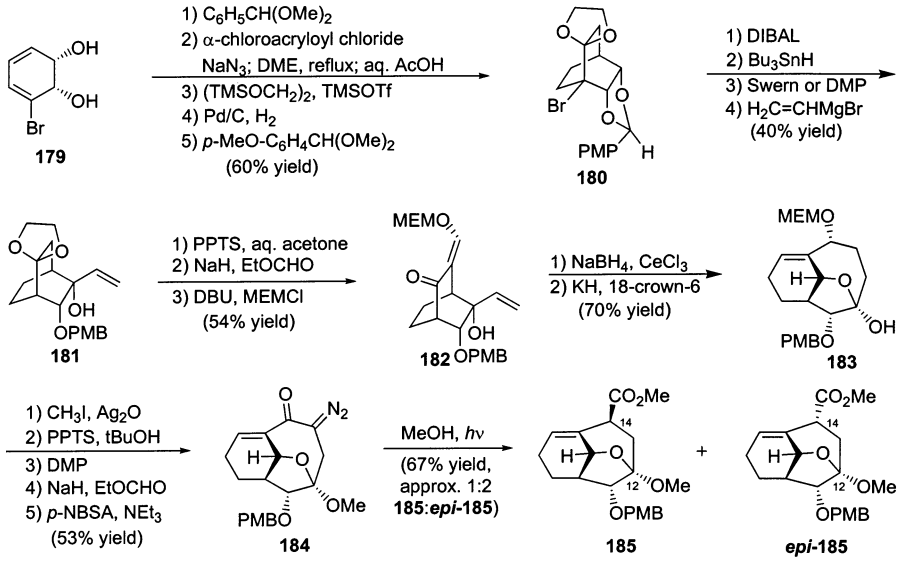
The synthesis commences with *cis*-bromocyclohexadiene diol **179**, which, after a Diels−Alder, Curtius rearrangement sequence, double bond reduction, and intervening protecting group chemistry, yields **180**. This compound is treated with DIBAL to effect regioselective protecting group migration, debrominated, oxidized, and alkylated with vinyl Grignard to yield **181**. The next task is to set up a formylation to provide a 1,5-diene necessary for the oxy-Cope rearrangement. This is accomplished by removing the dioxolane protecting group in **181**, formylating at the α-position of the newly unmasked ketone functionality, and converting the resulting *β*-keto aldehyde to MEM enol ether **182**. Upon reduction of the C10 ketone under Luche conditions, the system is poised to undergo a [3,3]sigmatropic rearrangement. This proceeds smoothly on heating in the presence of KH and 18-crown-6 to provide **183**.

The ensuing five-step sequence, which provides the α-diazoketone substrate (**184**) for the Wolff ring contraction, involves two protecting group manipulations and an oxidation step and culminates in a two-step deformylative diazotization sequence. When subjected to photolysis in MeOH, **184** undergoes the desired ring contraction in high yield, generating approximately a 1:2 mixture of desired bicycle **185** and its C14 epimer, *epi*-**185**. This sequence generates the desired bicyclic skeleton in an efficient manner, and the authors go on to propose a strategy for the regio- and diastereoselective introduction of the phomoidride C1−C8 and C18−C25 side chains utilizing a 5-*exo*-trig radical cyclization and capture method. It is further proposed that one of the previously employed methods for formation of the maleic anhydride moiety will be adopted, utilizing the ketone oxidation state at C12.

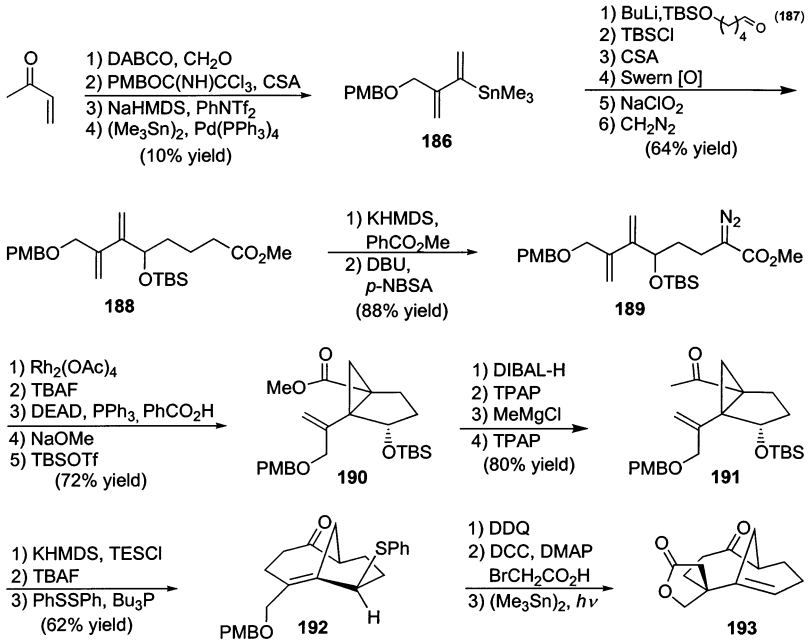
Kyriacos C. Nicolaou and Colleagues. In addition to his type II IMDA approach that is described above (see Section II.B.1), Nicolaou and co-workers explored a different approach based upon a divinylcyclopropane rearrangement (Scheme 35).[62] To this end, methyl vinyl ketone was converted to stannane **186**. Following the addition of **186** to aldehyde **187**, oxidations and functional group manipulations yielded diene **188**. Diazo ester **189** was then synthesized according to Taber's protocol and subjected to intramolecular cyclopropanation conditions employing $Rh_2(OAc)_4$ as catalyst. The resulting vinyl cyclopropane was manipulated via a Mitsunobu inversion sequence and protecting group alterations to give ester **190**. This compound was then converted to ketone **191**, whose silyl enol ether underwent smooth divinylcyclopropane rearrangement, followed by facile conversion to phenyl sulfide **192**. To address the quaternary center in this model system, Nicolaou employed a 5-*exo*-dig radical cyclization−elimination sequence. Conversion of **192** to the bromoacetate ester followed by photolysis in the presence of $(Me_3Sn)_2$ furnished spiro lactone **193**. Because this compound possessed the incorrect relative stereochemistry at the C14 quaternary center and because the IMDA route (Section II.B.1; Scheme 9) proved more fruitful for synthetic studies, no further advances have been reported using this system.[70]

Huw M. Davies and Colleagues. Davies and coworkers employ a type II intramolecular [3+4] cycloaddition strategy to construct the phomoidride carbocyclic core (Scheme 36).[108−110] This sequence utilizes easily accessible diazo compound **195** as the substrate for its key transformation, and after a series of steps, the route elegantly provides bicyclo[4.3.1]deca-1,6-diene **199**. In the event, furan aldehyde **194** was treated with the dianion of acetylacetone followed by diazo transfer to give **195**. Upon TIPS enol ether formation and diazo decomposition, the resulting rhodium carbenoid underwent a tandem cyclopropanation−vinylcyclopropane rearrangement. Treatment with NBS (to stabilize the [3+4] adduct) gave rise to ketone **196**. As part of installing the bridgehead olefin, **196** was reduced and its silyl enol ether deprotected to give **197**. The stage was now set for a *β*-elimination similar to that employed by

Scheme 34. Banwell's Approach to the Phomoidride Core Structure



Scheme 35. Nicolaou's Divinyl−Cyclopropane Rearrangement Approach



Danishefsky in his total synthesis. Hydrogenation to remove both the bridgehead olefin and the tertiary bromide, equilibration of C11 isomers, mesylate formation, and β-elimination furnished tetrahydrofuran **198**. This was opened with TMSOTf, and the resulting alcohol was eliminated using silica, thus giving Davies' most advanced product (**199**). This compound contains the bridgehead double bond found in the phomoidrides and other pendant functionality perhaps sufficient for advancement to the natural products.

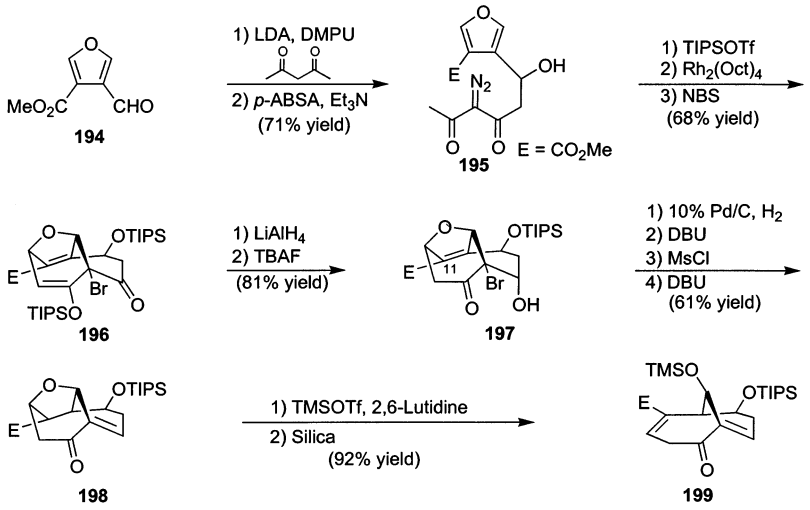
3. Routes Involving Aldol Type Disconnections

In addition to the aldol disconnection employed by the Danishefsky group in their total synthesis of the phomoidrides, two other aldol type disconnections have been proposed. These come from the groups of Alan Armstrong at the University of Nottingham in England, and an enamine approach from Samuel Danishefsky at the Sloan-Kettering Institute for Cancer Research in New York City.

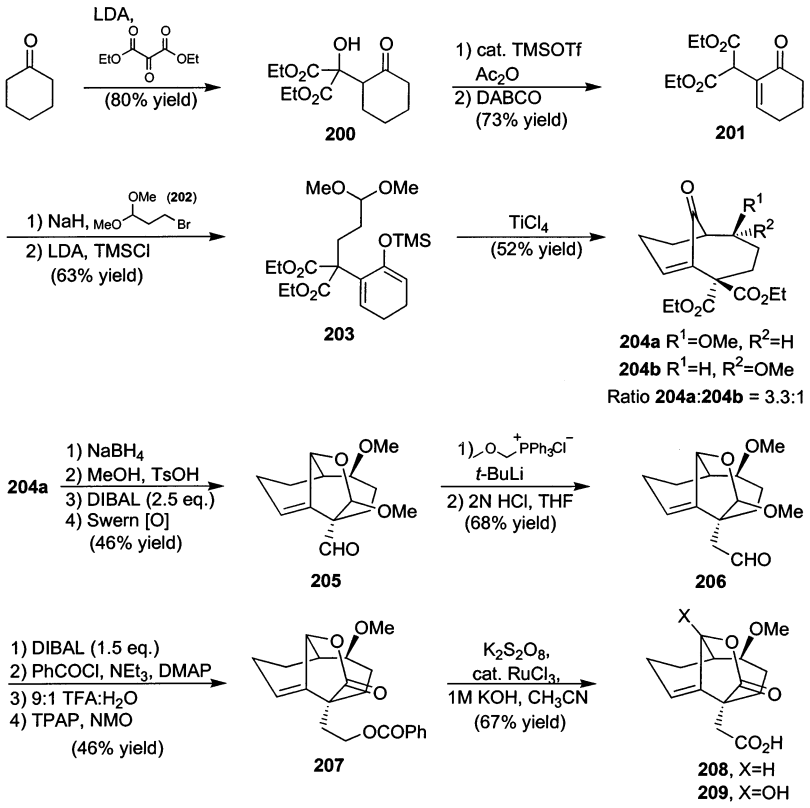
Alan Armstrong and Colleagues. Alan Armstrong and co-workers at the University of Nottingham in England have studied a Mukaiyama aldol reaction to construct the bicyclic phomoidride ring system.[111−113] As shown in Scheme 37, they began by treating the lithium enolate of cyclohexanone with diethyl oxomalonate to give aldol product **200**. A two-step elimination/isomerization sequence was used to install the requisite enone **201**, which was alkylated with bromide **202**. The resulting ketone was converted to its silyl enol ether to give diene **203**. This intermediate is poised to undergo a $TiCl_4$-promoted intramolecular Mukaiyama aldol reaction to provide the phomoidride ring system (**204**) in six steps from cyclohexanone.

The most recent paper from the Armstrong group details the elaboration of diastereomer **204a** to

Scheme 36. Davies' Route to the Phomoidrides



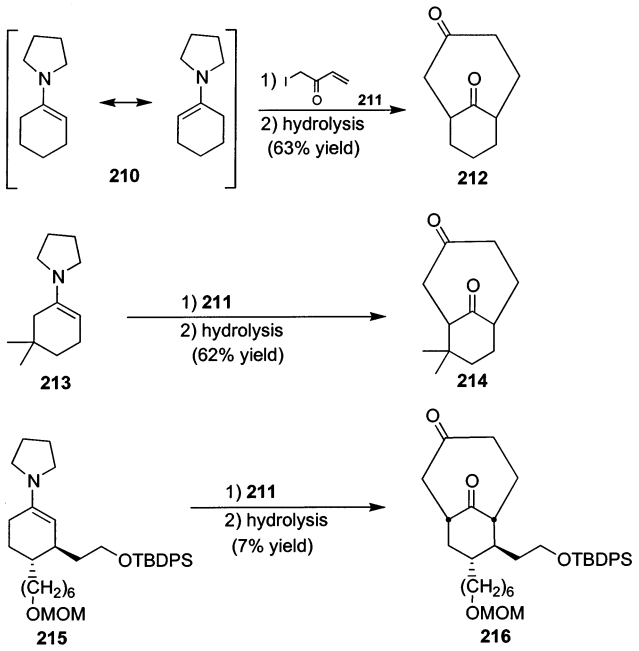
Scheme 37. Armstrong's Route to the Phomoidrides



include the phomoidride C14 quaternary center and γ-hydroxy lactone functionalities.[113] Thus, treatment of ketone **204a** under Luche conditions gave rise to diastereoselective ketone reduction, lactonization into the "top face" ethyl ester, and lactone reduction. The resulting lactol was protected as its methyl acetal, and the remaining "bottom face" ethyl ester was converted to an aldehyde to give **205**. One-carbon extension of this aldehyde with methyoxymethylphosphonium ylide followed by chemoselective hydrolysis provided homologated aldehyde **206**. This was then reduced, and the resulting hydroxyl was protected as its benzoate ester. Conversion to desired lactone **207** was accomplished via acetal deprotection and TPAP oxidation. Finally, treatment of **207** with basic $K_2S_2O_8$ and catalytic $RuCl_3{-}xH_2O$ provided benzoyl-deprotected acid **208** and small quantities of the corresponding pseudoacid **209**. Unfortunately, **209**, a compound that contains both the C14 quaternary center and the γ-hydroxy lactone found in the natural product, was not produced in appreciable quantities via this route. Optimization of the final oxidation step to improve the yield of **209** will provide an advanced model compound lacking only the maleic anhydride and the C1−C8 and C18−C25 side chains found in the phomoidrides.

Samuel J. Danishefsky and Colleagues. Danishefsky explored an alternative approach to the phomoidrides in which he studied the α,α'-annulation reactions of enamines with chloromethyl and iodomethyl vinyl ketones.[16] Shown in Scheme 38 are representative examples. Enamine **210**, derived from

Scheme 38. Danishefsky's Enamine Route to the Phomoidride Skeleton



cyclohexanone, underwent the desired annulation sequence in good yield giving **212**. A preliminary study with unsymmetrical enamine **213**, derived from 3,3-dimethylcyclohexanone, was found to give a good yield of the desired regioisomeric annulation product (**214**). However, attempts to reproduce these results with more appropriately substituted unsymmetrical cyclohexanones met with limited success. For example, enamine **215** gave only a very low yield of the desired bicycle **216**. Because of the low yields of bicyclic products obtained from these reactions, the Danishefsky group abandoned this route in favor of their aldol-Heck strategy (see Section II.C.4 above).

4. Carbon–Carbon Bond Fragmentation Strategies

The three fragmentation strategies discussed below involve the relatively late stage introduction of the C15−C16 bridgehead double bond, and utilize radical and photochemical means to construct relatively strained, complex polycyclic structures. This embedded ring strain provides the thermodynamic impetus for fragmentation reactions to reveal a latent phomoidride core structure. Contributions from Hiroto Nagaoka at Meiji Pharmaceutical University, Michael T. Crimmins at the University of North Carolina at Chapel Hill, John L. Wood at Yale University, Yoshiji Takemoto at Kyoto University, and Goverdhan Mehta at the Indian Institute for Scientific Research are summarized below.

Hiroto Nagaoka and Colleagues. Professor Hiroto Nagaoka and co-workers at Meiji Pharmaceutical University in Japan were the first group to report a fragmentation strategy toward the total synthesis of the phomoidrides.[114,115] In the past, Professor Nagaoka has extensively employed a sequential Michael addition strategy to build bicyclo[2.2.2]octane-derived systems.[116,117] His approach toward the phomoidrides also utilized this strategy (Scheme 39). Following a sequential Michael reaction between (*S*)-carvone (**217**) and (*E*)-methyl 4-benzyloxycrotonate, allylic chlorination furnished bicycle **218**. Reductive cyclization with samarium diiodide followed by protection of the resulting tertiary alcohol gave **219**, which, after reduction, ozonolysis, and Baeyer−Villiger oxidation, resulted in lactone **220**. Photolytic olefination of **220** gave three products (**221**−**223**), of which **221** was desired. Conversion of side product **222** into **221** was accomplished in excellent yield with Zn in AcOH.

Advancement of olefin **221** is shown in Scheme 40. Oxidation, reduction, and protecting group manipulations furnished intermediate **224**, which was selectively alkylated, reduced, and eliminated to give lactone **225**. Further functional group manipulations then gave rise to pinacol precursor **226**. Pinacol coupling of **226**, followed by β-elimination and oxidation, provided intermediate **227**, thereby setting the stage for the introduction of the quaternary center.

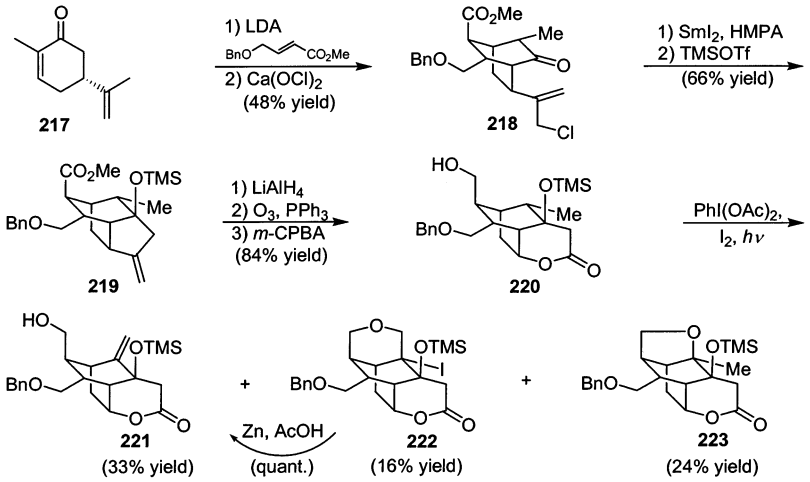
Nagaoka then applied Stork's bromoacetal chemistry to build the quaternary center. After Luche reduction and application of an α-bromo ethyl acetal, a 5-*exo*-trig radical cyclization gave rise to intermediate spiroacetal **228**. Fragmentation and olefin installation was accomplished by reaction of alcohol **228** under Suarez conditions to yield iodide **229**, followed by reductive olefination to introduce the bridgehead double bond. This provided Nagaoka's most advanced intermediate (**230**). This substrate possesses the C14 quaternary center and appropriate precursor structures for the eventual elaboration of maleic anhydride and side chain portions of the phomoidrides.

Michael T. Crimmins and Colleagues. The Crimmins group has applied a heteroatom-tethered [2+2] photocycloaddition strategy toward the synthesis of the phomoidride core (Scheme 41).[118] This approach allows access to a crossed photoadduct (e.g., **234**) with high regioselectivity, and a subsequent deoxygenative radical fragmentation unravels the phomoidride core.

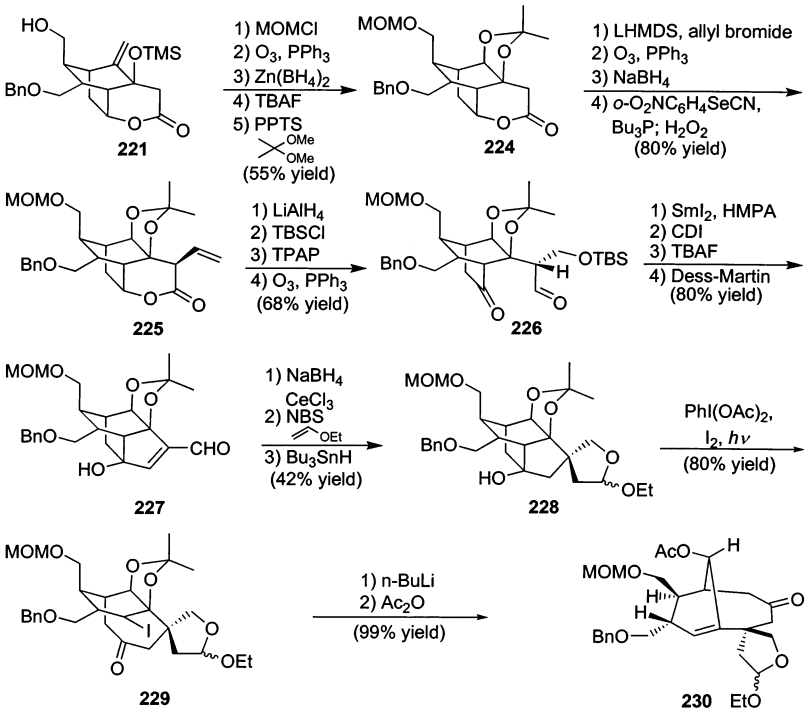
The synthesis starts with 4-penten-1-ol, which is subjected to standard conditions to provide ynoate **231** (Scheme 41). This is converted to cyclopentenone **233** on treatment with $ZnCl_2$, CuBr, and cyclopropane **232** using a homoenolate addition methodology developed in the Crimmins laboratory.[119] Compound **233** is then subjected to ring-closing metathesis (RCM) conditions using Grubbs' catalyst to provide a seven-membered cyclic ether. This intermediate can be converted almost exclusively (94:6) to crossed photocycloadduct **234** on treatment with ultraviolet light. The tetrahydrofuran ring is then opened with $PhSeSiMe_3$ and ZnI_2, and trapped with acetic anhydride to give **235**. Olefin formation, epoxidation, thiocarbamate installation, and radical fragmentation unravel the phomoidride skeleton (**236**). One might imagine elaborating the C11−C12 β-ketoester found in **236** into the maleic anhydride, but this substrate lacks functionality for the incorporation of the C14 quaternary center and side chain portions of the natural product.

John L. Wood and Colleagues. Work in the Wood laboratories has centered upon the rapid construction of a bicyclo[2.2.2]octane skeleton in

Scheme 39. Nagaoka's Approach to the Phomoidrides, Part I



Scheme 40. Nagaoka's Approach to the Phomoidrides, Part II

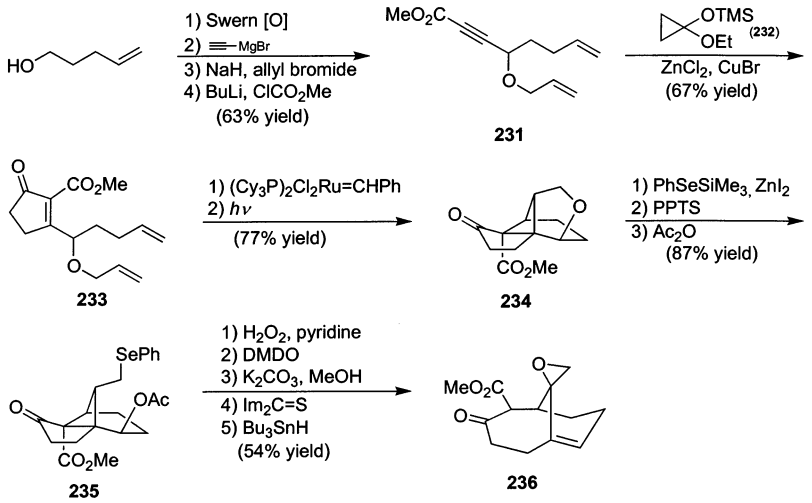


order to effect a late stage carbon−carbon bond fragmentation to unravel the phomoidride core (Scheme 42). Initial model studies demonstrated that simple norbornane (**238**) and isotwistane (**241**) core structures could serve as substrates for Wharton fragmentation reactions, both generating bicyclic-[4.3.1] skeletons quickly and efficiently.[17]

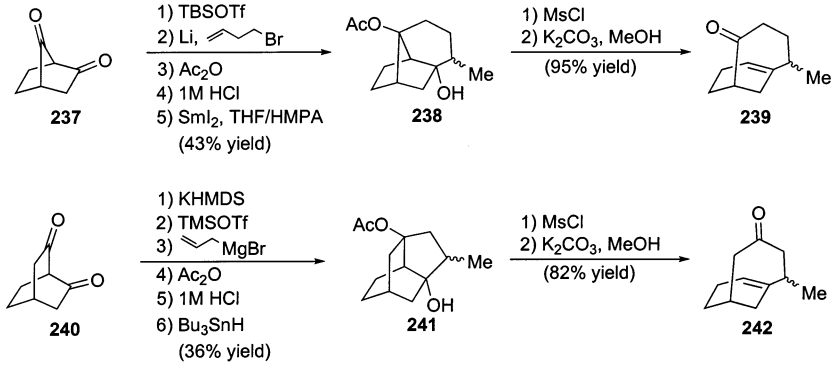
The norbornane substrate was prepared starting with diketone **237**. This was converted to its TBS enol ether, regioselectively alkylated with homoallyllithium, acetylated, deprotected, and coaxed to undergo a 6-*exo*-trig ketyl radical cyclization with samarium diiodide to yield norbornane **238**. Upon mesylation of the derived tertiary alcohol and acetate hydrolysis, oxyanion-initiated Wharton fragmentation took place in situ at room temperature to provide **239** in high yield. A similar sequence was employed for the construction of the isotwistane system. Thus, known bicyclic diketone **240** was converted to isotwistane **241**, which, when subjected to the mesylation acetate hydrolysis sequence, gave bicycle **242**. Note that both the norbornane and the isotwistane skeletons provided isomeric [4.3.1] bicyclic products upon fragmentation, which differed only in the position of the derived ketone functionality. Therefore, it was reasoned that a rapid route to either norbornane or isotwistane type precursors would supply appropriate substrates for further elaboration.

Initial efforts focused on obtaining access to isotwistane type structures.[120] A major rationale for this choice resided in the range of possible Diels−Alder disconnections offered by the bicyclo[2.2.2]octane core, which can be advanced to the isotwistane by a variety of methods. Indeed, a model isotwistane (**248**; Scheme 43) could be synthesized employing Wessely oxidation chemistry (**245** → **247**) followed by a thermal Diels−Alder reaction (**247** → **248**), but undesired reaction products (**246**) predominated through this route.

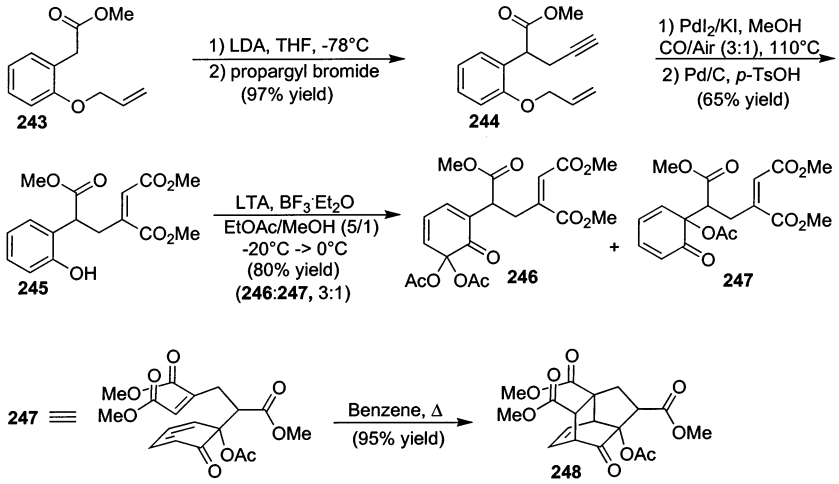
Scheme 41. Crimmins' Photocycloaddition−Fragmentation Approach



Scheme 42. Wood's Fragmentations of Norbornane and Isotwistane Skeletons

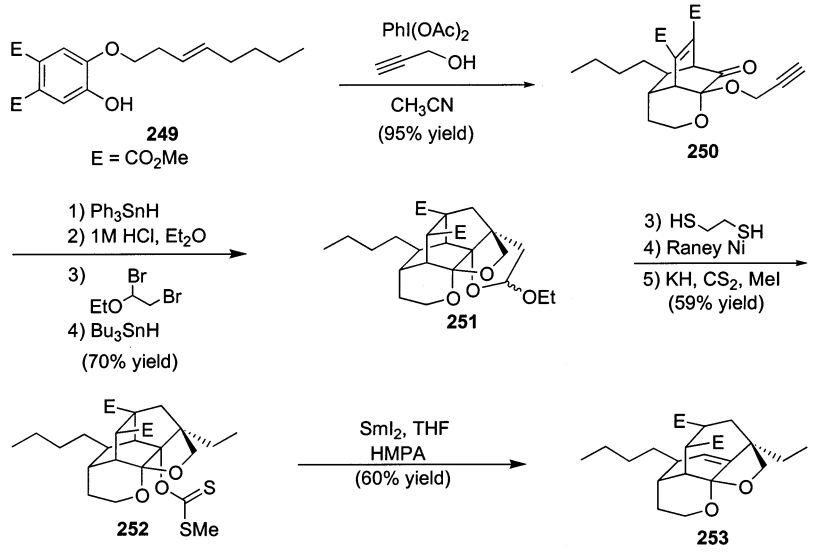


Scheme 43. Wood's Wessely Oxidation Approach to the Isotwistane Ring System

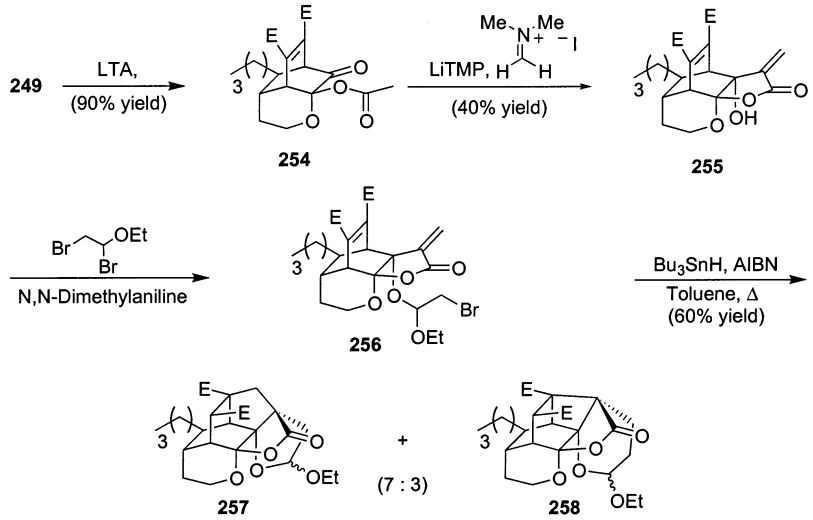


A more synthetically useful approach to the isotwistane skeleton was finally realized in the development of a tandem aromatic oxidation−IMDA reaction detailed in Scheme 44 (**249** → **250**).[120] This reaction allowed for the one pot assembly of a densely functionalized [2.2.2] bicyclic core structure, which could rapidly be elaborated into various isotwistane fragmentation substrates. In an initial approach using this method, ether **249** was converted in one pot to propargyl acetal **250**. This intermediate, when treated with triphenyltin hydride, protodestannylated, and derivatized as the Stork bromoacetal, underwent tandem 5-*exo*-trig-5-*exo*-trig cyclization on treatment with tributyltin hydride to provide **251** as a mixture of ethyl acetal diastereomers. This transformation led to the formation of two quaternary carbon−carbon bonds with complete diastereoselectivity at the three newly formed stereogenic centers. Ring opening with ethanedithiol, desulfurization, and derivatization as the corresponding xanthate afforded fragmentation precursor **252**. When treated with samarium diiodide and HMPA, **252** unraveled to yield the [4.3.1] bicyclic skeleton of the phomoidrides (**253**). This compound lacks only the oxidation states at C27 and C29, the

Scheme 44. Synthesis and Fragmentation of an Isotwistane Core Structure



Scheme 45. Installation of C27 Acid Oxidation State



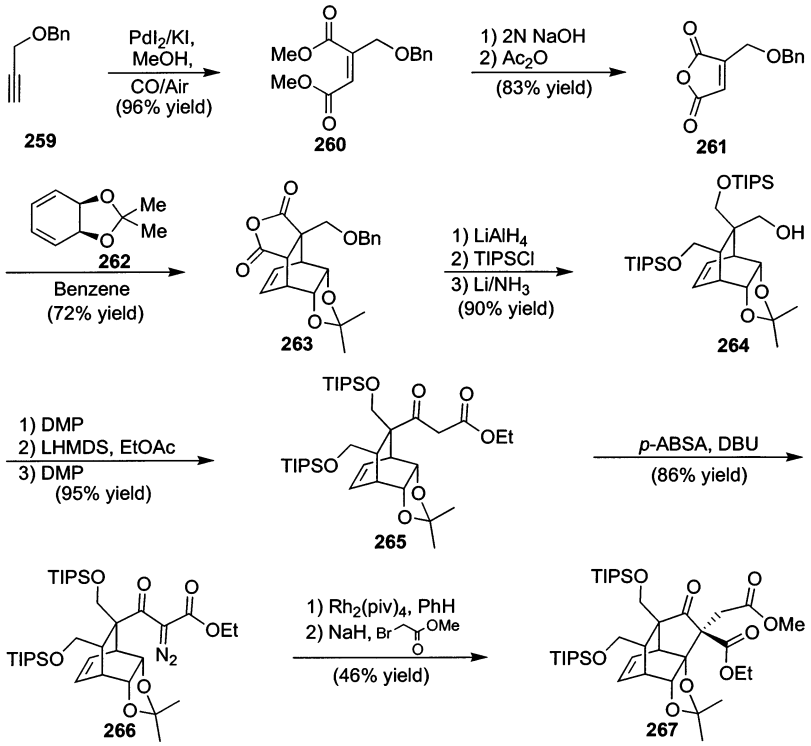
fully elaborated side chains, and the intact maleic anhydride moiety.

Incorporation of the C27 oxidation was made possible utilizing a $Pb(OAc)_4$-mediated tandem phenolic oxidation/Diels−Alder sequence (**249** → **254**; Scheme 45). A lactone ring closure−methylenation sequence was then accomplished on treatment of **254** with LiTMP and Eschenmoser's salt to form exo olefin **255**. As before, the tertiary alcohol was derivatized as its Stork bromoacetal (**256**), which, upon treatment with tributyltin hydride, gave rise to a favorable mixture of 5-*exo*-trig-5-*exo*-trig (**257**) and 6-*endo*-trig-4-*exo*-trig (**258**) cyclization products.

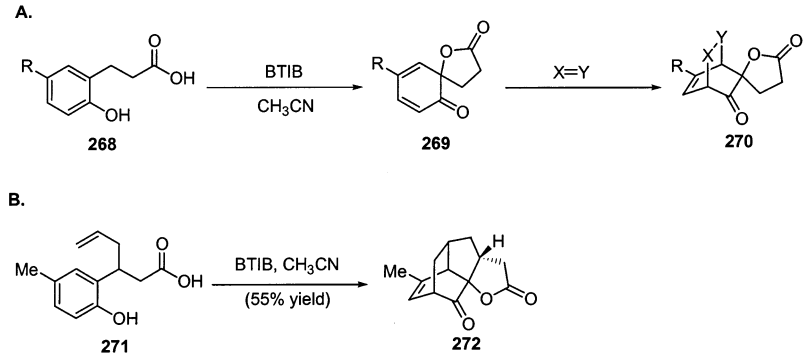
Simultaneously with oxidative dearomatization studies, a rhodium carbenoid-mediated C−H insertion approach to an isotwistane fragmentation precursor was explored (Scheme 46).[121] This approach began with the oxidative dicarbonylation of propargyl ether **259** to provide maleate **260**, and dehydration to the corresponding maleic anhydride (**261**). Subsequent Diels−Alder reaction with acetonide **262** yielded **263** as a single cycloadduct. This compound was exhaustively reduced to the corresponding diol, protected as its TIPS ether, and benzyl-deprotected to provide alcohol **264**. Then, by way of a three-step sequence, **264** was converted into β-ketoester **265** and smoothly diazotized to provide **266**. After screening a number of reaction conditions for the rhodium carbenoid-mediated C−H insertion reaction, it was discovered that the use of the $Rh_2(piv)_4$ catalyst system in benzene at 50 °C provided **267** as a single diastereomer after alkylation with methyl bromoacetate. Compound **267** contains the C14 quaternary center found in the natural phomoidrides, and while the fragmentation reaction to unravel the phomoidride core has not yet been performed on intermediates derived from this route, functionality is in place for elaboration of the maleic anhydride and olefinic side chain portions of the molecule.

Highlight: Novel Chemistry Developed in the Wood Group. After publishing the route to phomoidride model substrate **248**, Wood and colleagues went on to explore an intramolecular variant of their Wessely oxidation (see Scheme 43; **245** → **247**) in greater detail (Scheme 47).[122] Substrates tested were derivatives of 3-(2-hydroxyphenyl)propionic acid (**268**), which underwent aromatic oxidation and intramolecular trapping to yield intermediate spirolactone-

Scheme 46. Wood's Rhodium-Catalyzed C−H Insertion Route



Scheme 47. Wood Group's Phenolic Oxidation/Diels−Alder Methodology

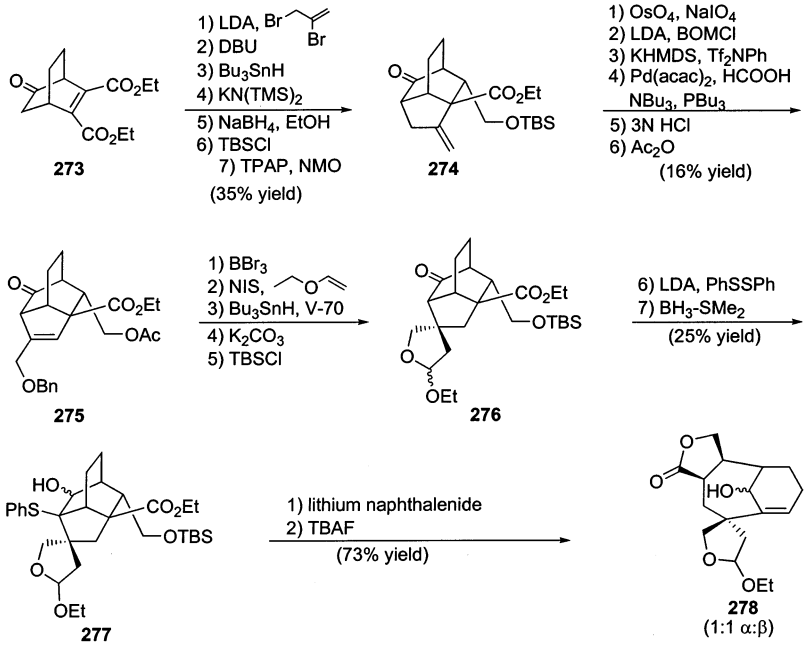


dienones **269** (Scheme 47A). These could then be reacted intermolecularly with both electron rich and electron poor dieneophiles (X = Y) to furnish bicyclo-[2.2.2]octanes (**270**) with high regiochemical control and in good to excellent yields. It was found that the reaction proceeded with inverse electronic demand; the reaction rate was greatly enhanced when performed with relatively electron deficient dienes and electron rich dienophiles. Finally, high levels of substrate-directed stereocontrol were achieved by incorporating chirality in β-alkylated propionic acid derivatives (Scheme 47B). Derivative **271** provided easy access to an isotwistane skeleton (**272**) as a single diastereomer. This compound is similar to that found in the Wood group's Wessely oxidation approach toward the phomoidrides (see **248**, Scheme 43).

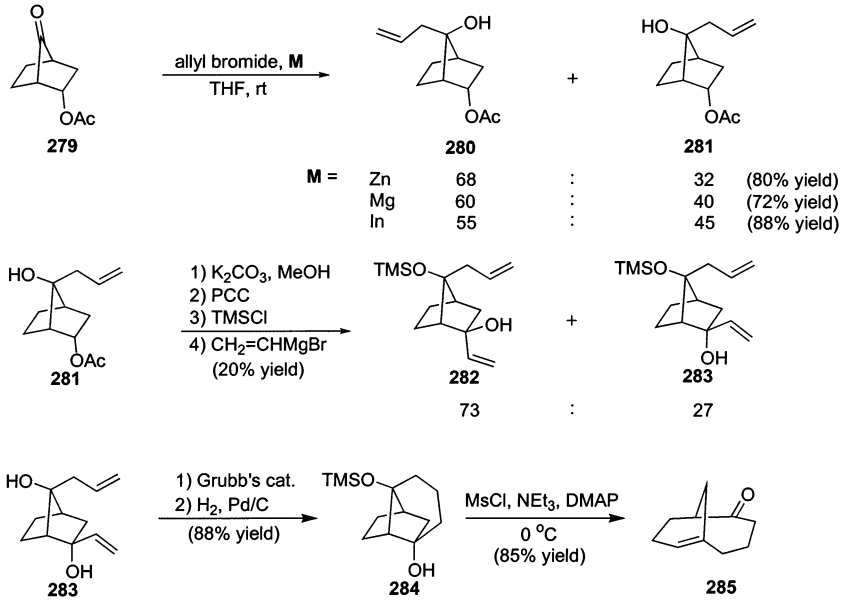
Yoshiji Takemoto and Colleagues. Professor Yoshiji Takemoto and co-workers at Kyoto University have recently put forth a route to phomoidride B that involves the reductive fragmentation of a bicyclo-[2.2.2]octane skeleton (Scheme 48).[123] In this approach, an anion driven fragmentation of an isotwistane proceeds to yield the phomoidride core skeleton containing the necessary functionality for conversion into the fully elaborated maleic anhydride and C14 quaternary center.

Their synthesis began with the treatment of known diester **273** with 2,3-dibromopropene, followed by epimerization, radical cyclization, and oxidation state manipulations to yield tricycle **274**. This compound then underwent oxidative olefin cleavage, alkylation with BOMCl, reductive olefination, and protecting group exchange to provide **275**. The stage was now set for introduction of the quaternary center. This was accomplished via the 5-*exo*-trig cyclization of an α-iodo ethyl acetal-derived radical to give a 1:1 mixture of diastereomeric tetracycles. The interconversion of a primary acetate to its corresponding TBS ether allowed separation of these diastereomers, one of which (**276**) was advanced (relative stereochemistry not determined). Introduction of the phenyl thiolate group and ketone reduction yielded fragmentation substrate **277** as a 1:1 mixture of hydroxyl diastereomers. Nevertheless, treatment of this mixture with lithium naphthalenide in THF at −78 °C,

Scheme 48. Takemoto's Approach to the Phomoidrides



Scheme 49. Mehta's Approach to the Phomoidride Skeleton



followed by silyl deprotection, yielded fragmentation product **278** in high yield as a mixture of diastereomers.

This sequence efficiently introduces the carbocyclic core, bridgehead olefin, and quaternary centers. Elaboration to form the maleic anhydride would require the routine installation of the maleate double bond and oxidation state adjustments. However, this route has not been able to provide ready access to the trans-disposed side chains found in the natural product.

Goverdhan Mehta and Colleagues. The most recent of the fragmentation approaches to the phomoidride carbocyclic core was put forth by Goverdhan Mehta and colleagues at the Indian Institute for Scientific Research.[124] This route, like that developed by the Wood group, involves the late-stage Wharton fragmentation of a 1,3-diol derivative to provide the phomoidride skeleton (Scheme 49). Their approach began with allylation of known norbornyl ketone **279** to provide a diastereomeric mixture of alcohols **280** and **281**. The diastereoselectivity of this reaction proved relatively insensitive to the type of allylmetal reagent used. Minor diastereomer **281** was then deprotected at the acetate, the resulting hydroxyl was oxidized to the corresponding ketone, and the remaining tertiary hydroxyl was protected as its TMS ether. Alkylation with vinyl Grignard took place predominantly on the less sterically hindered face of the norbornyl skeleton to provide a 73:27 ratio of **282**:**283** with the desired diastereomer being the minor component of the mixture. Nevertheless, **283** was subjected to RCM conditions with 30 mol % Grubbs' catalyst and hydrogenated to yield 1,3-diol derivative

284. Simple exposure of **284** to base provided the desired fragmentation product **285** in good yield. This type of alkylation−RCM−Wharton fragmentation approach is further extended by Mehta to give rise to other bridgehead olefin-containing structures aside from the phomoidride skeleton.

5. Biomimetic Strategies

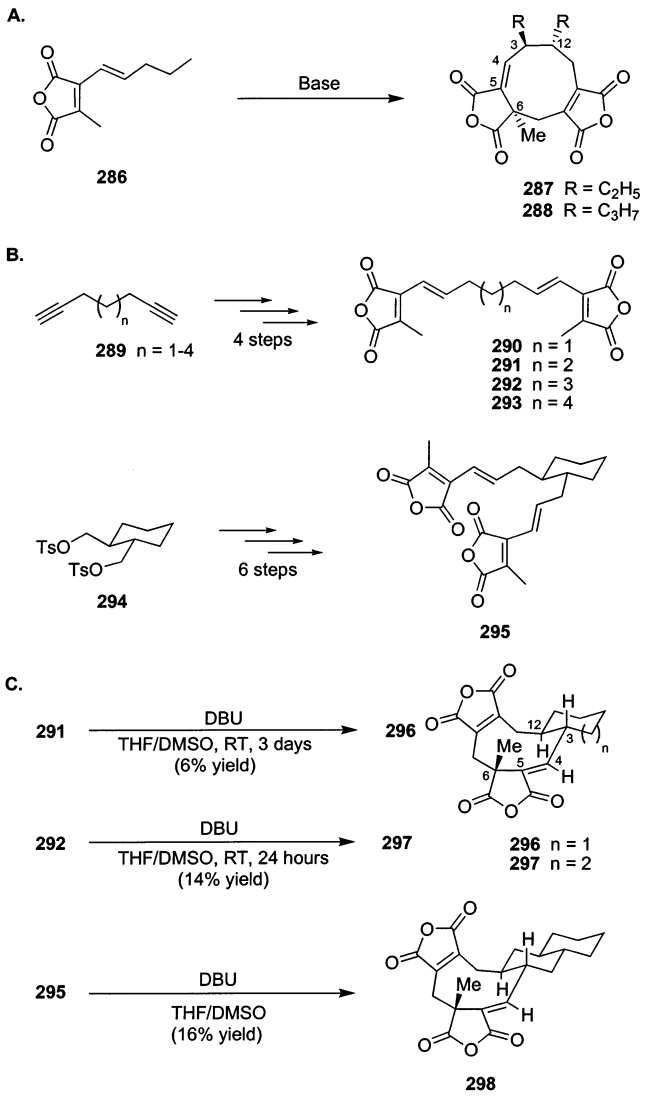
An appealing approach to the construction of the phomoidride core is to follow the example set forth by nature. It is thought that the phomoidrides are assembled biologically via the cascade dimerization of two anhydride units, and a suitably developed biomimetic system could hope to accomplish the assembly of the carbocyclic core in single chemical transformation. Both the laboratories of Jack Baldwin at Oxford University and Gary Sulikowski at Texas A&M University have published model studies in pursuit of such syntheses.

Jack Baldwin and Colleagues. Jack Baldwin and co-workers at Oxford University disclosed the first of the biomimetic approaches to the phomoidrides. Initial studies were based upon the work of Barton and Sutherland on the nonadrides glaucanic acid (**13**; see Section I.D, Scheme 1A) and *iso*-glaucanic acid (**287**)[11,36−39] and involved attempts to bring about the dimerization of anhydride **286** to form nonadride derivative **288** (Scheme 50A).[125] These studies confirmed earlier work by the Sutherland group on the structure of *iso*-glaucanic acid (**287**)[38,39] and emphasized the need to improve the dimerization reaction. Specifically, conditions were sought to minimize formation of undesired spiro-anhydride side products, control the relative stereochemistry between the C3 and the C12 alkyl groups, and direct the geometry of the C4−C5 double bond, which is present in the (*E*)-configuration in nonadrides **287** and **288** but has the (*Z*)-geometry in the phomoidrides (see **1**, C15−C16).

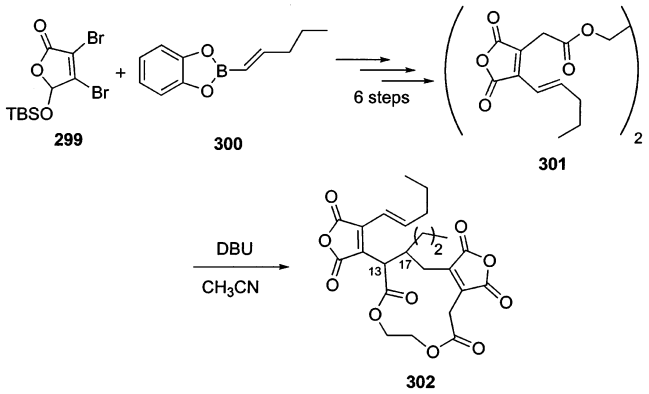
With these goals in mind, in their subsequent publication, Baldwin and co-workers synthesized tethered anhydrides **290**−**293** and **295** (Scheme 50B).[126] These compounds were accessed easily (four steps for **290**−**293** starting from terminal bis-acetylenes **289** and six steps for **295** starting from bis-tosylate **294**) and subjected to intramolecular cyclodimerization conditions. Acyclic molecules **291** and **292** gave rise to the corresponding dimerization products **296** and **297**, and cyclic bis-anhydride **295** gave rise to decalin-containing polycycle **298** (Scheme 50C). All three cyclodimerization products possessed the desired trans orientation between the C3 and the C12 alkyl side chains. However, the undesired syn relationship between the methyl group at C6 and the hydrogen at C3 and the undesired (*E*)-trisubstituted C4−C5 double bond geometry were obtained in all three compounds.

Gary Sulikowski and Colleagues. Sulikowski and colleagues have published approaches to phomoidride B which involve the dimerization of two suitably functionalized anhydrides, thus mirroring their biogenetic model (see Section I.D).[127,128] In initial studies (Scheme 51), a series of dimeric anhydrides (**301**) were synthesized with the hope of affecting an intramolecular dimerization cascade to make the C13−C14 and C9−C17 carbon−carbon bonds found in the natural products. While these substrates were accessed easily in six steps from a mucobromic acid derivative (**299**) and vinyl boronate (**300**), on treatment with DBU in acetonitrile, an undesired pathway was followed to yield products derived from an initial C13−C17 cyclization event (**302**). Other dimeric anhydride derivatives studied under various reaction conditions gave similarly derived products.

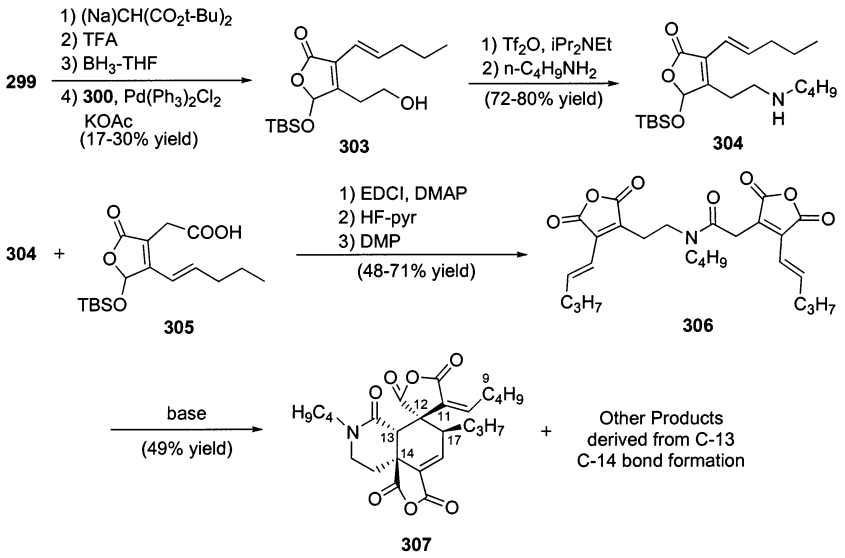
Scheme 50. Jack Baldwin's Biomimetic Studies



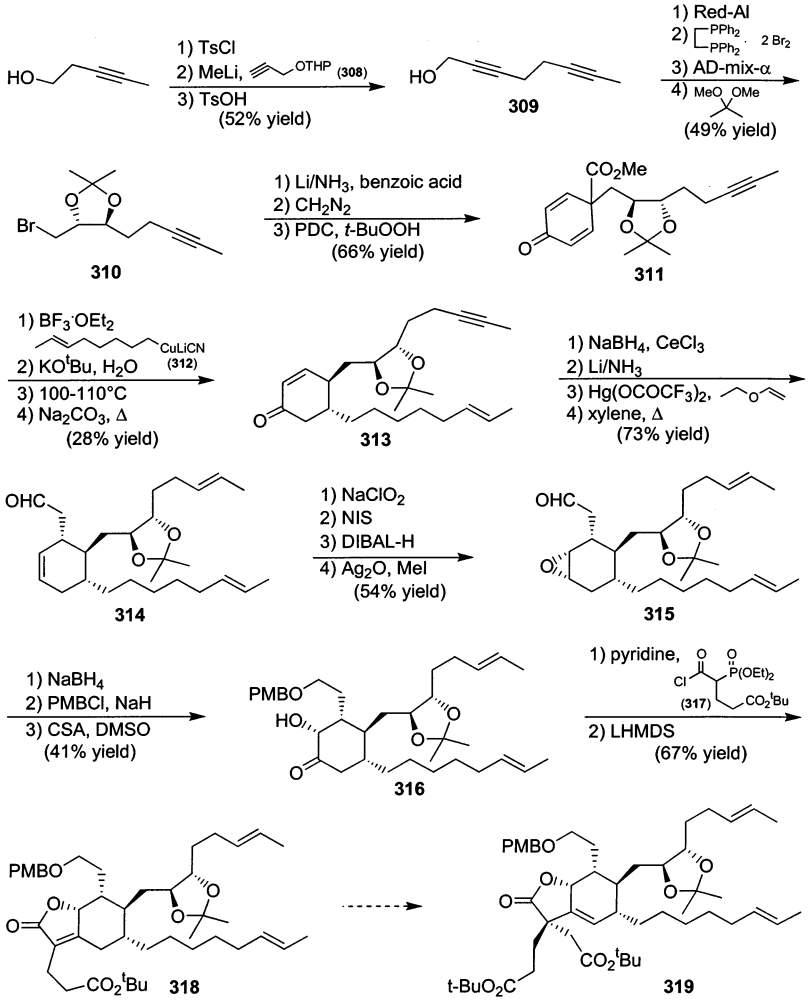
Scheme 51. Initial Homodimerization Attempts



Scheme 52. Formation of the C13−C14 Bond Using the Dimerization Approach



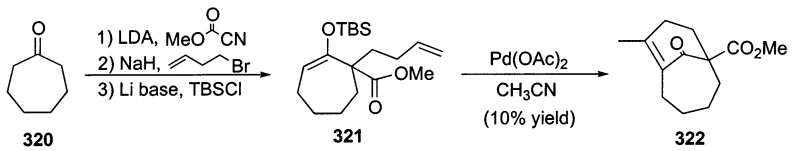
Scheme 53. Paquette's Progress toward the Phomoidrides



In a more recent approach (Scheme 52),[127] Sulikowski switched to a modified bisanhydride substrate containing a tertiary amide linkage (**306**). Their synthesis began once again with mucobromic acid derivative **299**, and after conversion to a monohydroxyethyl derivative, a Suzuki cross-coupling reaction provided anhydride **303**. This was converted via *n*-butylamine displacement of a primary hydroxyl-derived triflate to **304**, which, after TBS deprotection and oxidation, could be coupled to acid **305** to provide bisanhydride **306**.

Compound **306** did indeed undergo regioselective conjugate addition of a C13 enolate to C14 on treatment with base. However, the subsequent steps

Scheme 54. Toyota and Ihara's Cycloalkenylation Reaction



in the reaction sequence, which required the formation of a C9−C17 bond to arrive at the phomoidride core, led to products containing C11−C17 and C12−C17 carbon−carbon bonds. An X-ray crystal structure of **307** verified that the first Michael addition occurred with the expected exo approach of the anhydride units. Computational studies are provided to explain these observations.

6. Miscellaneous Strategies

Leo Paquette and Colleagues. Professor Leo Paquette and co-workers at The Ohio State University have also published efforts toward the phomoidrides.[129] Although they did not succeed in making the desired carbocyclic skeleton, they advanced quite far (Scheme 53). Starting with commercially available pent-3-yn-1-ol, activation and treatment with THP−ether **308** afforded diyne **309** after deprotection. Allylic reduction, bromination, asymmetric Sharpless dihydroxylation, and protection completed most of the first alkyl side chain in intermediate **310**. Acetylene **310** was then subjected to a reductive alkylation with benzoic acid under Birch conditions and further transformed into **311**. The second side chain component (**312**) was added to **311** as its cuprate, and the resulting mixture of diastereomers was converted in three steps into enone **313**. Luche reduction, acetylene reduction, and a Claisen rearrangement gave aldehyde **314**. This compound was converted to epoxide **315** via an iodolactonization sequence and carried on to give α-hydroxy ketone **316**. Ultimately, a two-step acylation, intramolecular Horner−Wadsworth−Emmons sequence gave butenolide **318**. Unfortunately, all attempts to effect the desired alkylation of **318** to **319** were unsuccessful. No further papers have appeared detailing progress on this approach.

Masahiro Toyota, Masataka Ihara, and Colleagues. An approach to the phomoidride[4.3.1] bicyclic core structure was recently reported by Toyota, Ihara, and co-workers at Tohoku University in Japan (Scheme 54).[130] This method involved the treatment of an enol silane containing a pendant olefin under Saegusa conditions to yield cycloalkenylation products. Following this procedure, **321**, which was prepared from the lithium enolate of cycloheptanone (**320**) in three steps, was treated with stoichiometric $Pd(OAc)_2$ in acetonitrile to yield bicyclo[4.3.1]decene (**322**), albeit in low yield. Cycloalkenylation reactions were also performed on substrates to give rise to the bicyclo[5.3.1]undecene skeleton found in taxol and other [*n*.3.1] bicycles.

III. Conclusion

The circuitous road toward the syntheses of the phomoidrides is paved with discovery, invention, and adventure. However, the efforts presented herein should highlight not only the creativity and industriousness of the investigators but also the value of their pursuit. Endeavoring to synthesize complex natural products provides an impetus for the discovery of novel chemical techniques and mechanistic proposals, which in turn deliver an increased understanding of the behavior of chemical systems. It is therefore here, in the labyrinth of total synthesis, that the field of chemical science is advanced.

IV. References

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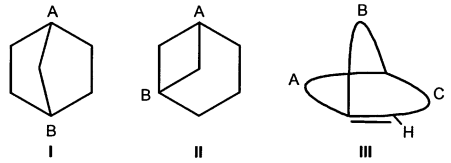

containing [2.2.1] and [3.1.1] systems. Later, efforts to extend Bredt's rule to describe the stabilities of bicyclo[x.y.z] alk-1-enes in general led to the proposal of a number of modified forms of the rule. One simple revision was put forth by Wiseman in 1967,[b] which is, for the most part, consistent with experiment: here, it is pointed out that all bridgehead double bonds in bicyclic systems are endocyclic to two of the rings (see **III**), "the strain of bridgehead alkenes is closely related to the strain of *trans*-cycloalkenes." The bridgehead double bond found in the phomoidrides is trans in a nine-membered ring and is therefore predicted to be stable, isolable, and, by this designation, not "anti-Bredt." Adapted from (a) Bredt, J.; Thouet, H.; Schmitz, J. *Annalen* **1924**, *437*, 1. (b) Wiseman, J. R. *J. Am. Chem. Soc.* **1967**, *89*, 5966. (c) Wiseman, J. R. *Angew. Chem. Int. Ed.* **1973**, *12*, 464.
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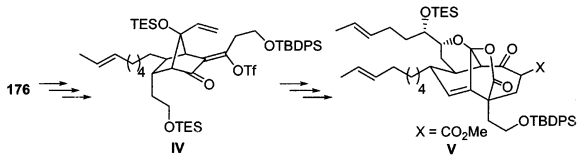

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