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Synthetic approaches to natural products

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Synthetic approaches to natural products

by

John Herman Malpert

A dissertation submitted to the graduate faculty

in partial fulfillment of the requirements for the degree of

DOCTOR OF PHILOSOPHY

Major: Organic Chemistry

Major Professor: George A. Kraus

Iowa State University

Ames, Iowa

1997

Graduate College
Iowa State University

This is to certify that the Doctoral dissertation of

John Herman Malpert

has met the dissertation requirements of Iowa State University

Signature was redacted for privacy.

Major Professor

Signature was redacted for privacy.

For the Major Program

Signature was redacted for privacy.

For the Graduate College

DEDICATION

To my family, for their understanding, patience and love.

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GENERAL INTRODUCTION

The ultimate goal of the synthetic natural products chemist is to synthesize complex natural products from simple inexpensive starting materials, using routes that are as efficient as possible. To complete this task, the synthetic chemist uses a vast array of known reactions that have been discovered by other scientists. In addition, the synthetic chemist should try to improve the aforementioned reactions, applying them to new systems and testing their limits and boundaries. Sometimes the synthetic chemist may be called upon to develop a reaction of his or her own to solve an intriguing synthetic problem. To accomplish the goal, the synthetic chemist must not only rely on his or her synthetic knowledge, but on his or her mechanistic knowledge as well, incorporating all the disciplines of organic chemistry into the problem solving process.

The purpose of this research was to create new routes to complex and biologically useful natural products. Three projects were undertaken to develop efficient routes to eburnamonine, MS-444 and halenaquinone.

In the first project, we worked on the synthesis of eburnamonine, a pentacyclic alkaloid that was first synthesized by Wenkert in 1965.[1] Our goal was to invent a more efficient route to the core structure which could be applicable to other molecules of similar nature. Our route involved the use of a novel nucleophilic addition of a metallated pyridine to an imine. We then extended this same methodology to the synthesis of a variety of indolo[2,3-*a*]quinolizine alkaloids.

In the second project, we set out to synthesize MS-444, a compound that was recently discovered from the culture broth of a bacterial strain.[2] In this project, we developed a method of synthesizing a highly-functionalized furan. This furan was then alkylated and further manipulated to produce the core structure of MS-444.

In the third project, we worked on halenaquinone, a natural product which exhibits biological activity and has been isolated from marine sponges in the Indian

and Pacific Oceans.[3] Only one total synthesis of this compound has been reported and that was by Harada and co-workers in 1988.[4] Upon our undertaking of this project, we developed a direct approach to the halenaquinone skeleton which involved the use of a photochemical hydrogen atom abstraction followed by a [4+2] cycloaddition.

Dissertation Organization

This dissertation was written so that each chapter represents a publishable article. Therefore, the numbering scheme adopted for the compounds and the references are independent for each paper.

References

1. Wenkert, E.; Wicksburg, B. *J. Am. Chem. Soc.* **1965**, *87*, 1580.
2. Nakanishi, S.; Chiba, S.; Yano, H.; Kawamoto, I.; Matsuda, Y. *J. Antibiot.* **1995**, *48*, 948.
3. Roll, D. M.; Scheuer, P. J.; Matsumoto, G. K.; Clardy, J. *J. Am. Chem. Soc.* **1983**, *103*, 6177.
4. Harada, N.; Sugiokia, T.; Ando, Y.; Uda, H.; Kuriki, T. *J. Am. Chem. Soc.* **1988**, *110*, 8483.

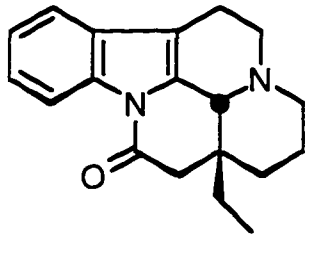
CHAPTER 1. A SYNTHETIC APPROACH TO EBURNAMONINE AND INDOLO[2,3-*a*]QUINOLIZINE ALKALOIDS

A paper, a portion of which was submitted to Synlett.

George A. Kraus and John H. Malpert

Introduction

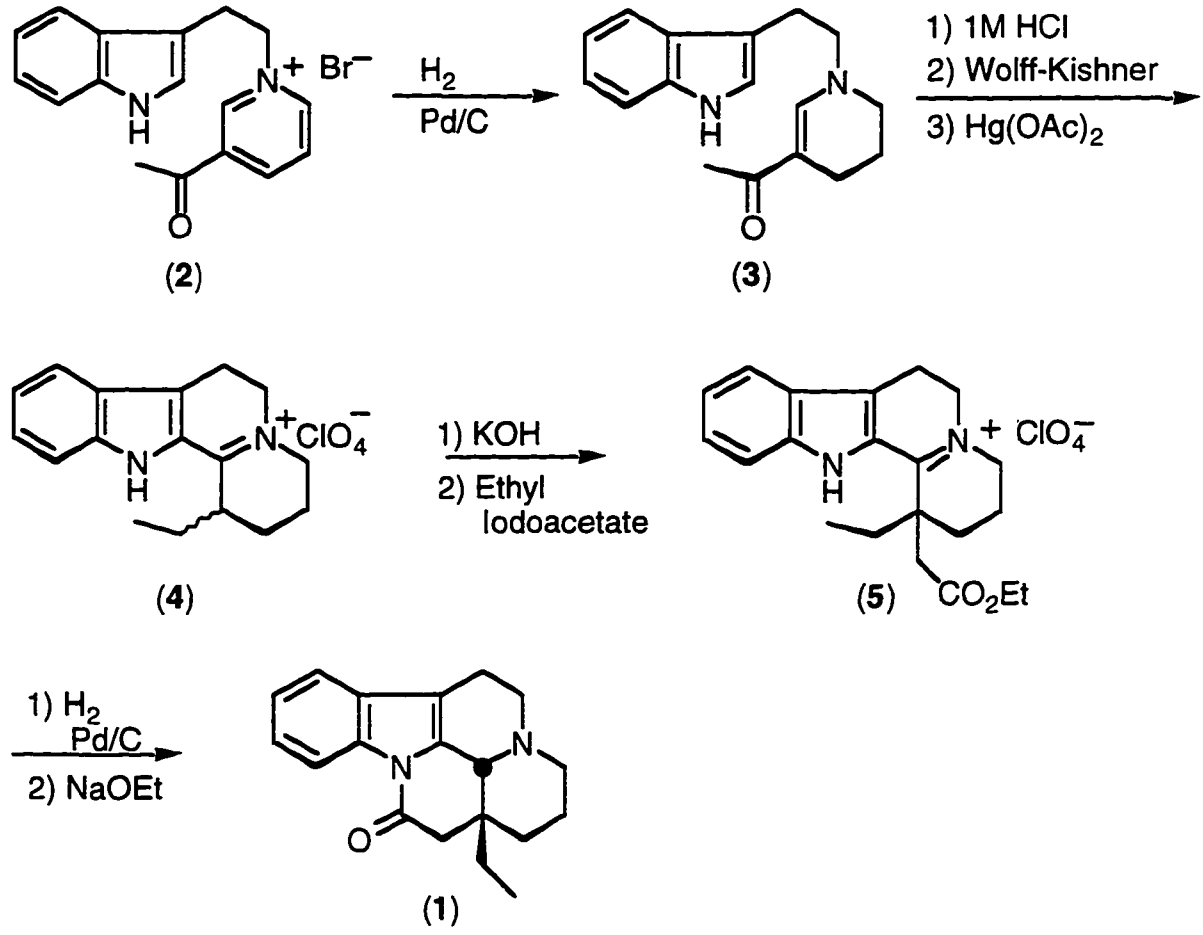
The pentacyclic skeleton of the indole alkaloid eburnamonine (1) has received considerable attention from synthetic chemists over the past 30 years. Eburnamonine was first isolated from the African apocynaceous plant *Hunteria eburnia* in 1960 by Barlett and Taylor.[1] Since that time, it has been shown to be a useful cerebrovascular agent.[2] Barlett and Taylor originally assigned the stereochemistry at the ring juncture to be trans. In 1965, Ernest Wenkert and co-workers completed the first synthesis of racemic eburnamonine, and they established that the correct stereochemistry was indeed cis.[3] Since that time, eburnamonine has been synthesized on numerous occasions with the most recent being in 1994 by Grieco[4a] and Palmisano.[4b]



(1)

The original synthesis of eburnamonine by Wenkert employed a Pictet-Spengler cyclization as its key step. Since that time, the majority of the syntheses involving this molecule have involved the use of a Pictet-Spengler or Bischler-Napieralski cyclization as their key step. As a consequence, many of the aforementioned syntheses have led to a mixture of eburnamonine and *epi*-eburnamonine, which contains the trans ring fusion.

Scheme I



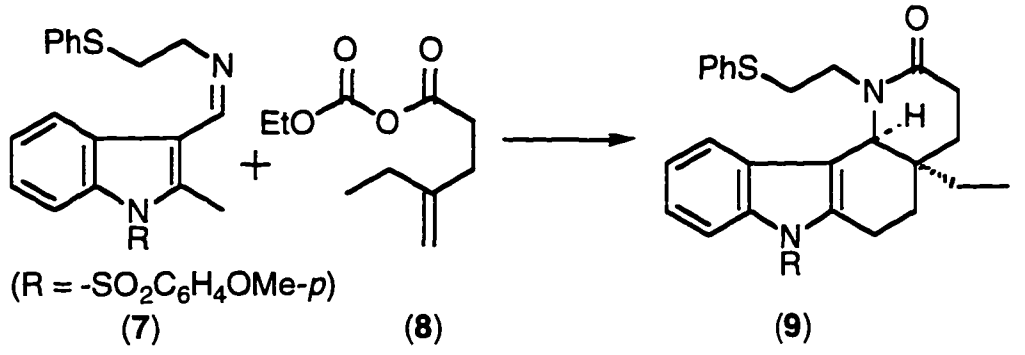
The original synthesis (Scheme I) of *dl*-eburnamonine by Wenkert began with compound (**2**), which was easily prepared from 3-acetylpyridine and 3-(2-bromoethyl)indole. Hydrogenation over palladium-charcoal yielded predominately the tetrahydro product (**3**), which underwent a Pictet-Spengler cyclization upon addition of 1M hydrochloric acid. A Wolff-Kishner reduction eliminated the ketone

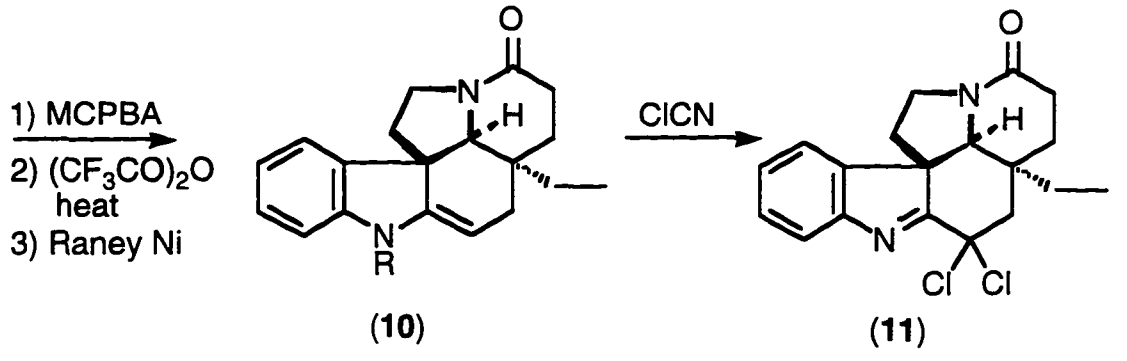
to provide the ethyl substituent, and oxidation with mercuric acetate provided the corresponding iminium salt (**4**). Treatment of this perchlorate salt with base and subsequent addition of ethyl iodoacetate provided the desired alkylated product (**5**), which was isolated once again as a perchlorate salt. Hydrogenation of the iminium salt (**5**) provided a mixture of stereoisomers which were carried on without further purification. Cyclization was achieved by treating the esters with sodium ethoxide to provide eburnamonine (**1**) and its trans isomer in an eight to one ratio.

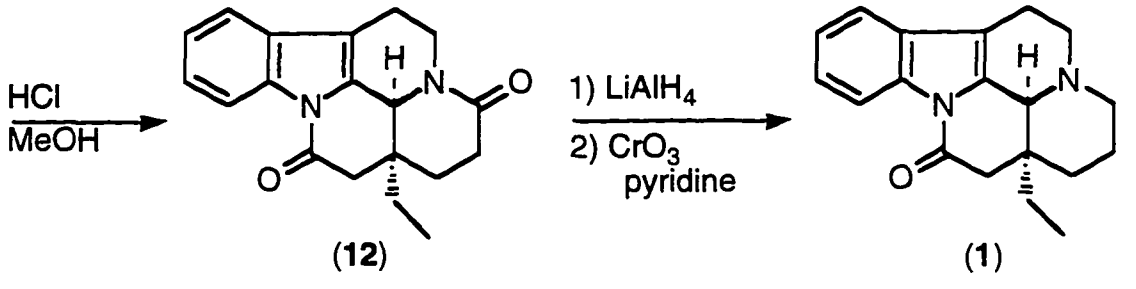
As was mentioned earlier, most of the syntheses involving eburnamonine employed either a Pictet-Spengler or Bischler-Napieralski cyclization as their key step. However, two exceptions should be noted. The first of these exceptions (Scheme II) was done by Philip Magnus and co-workers at Indiana University in 1986.[5] Magnus employed a novel rearrangement as his key step towards the transformation of eburnamonine. Initially compounds (**7**) and (**8**) were heated together to form the tetracyclic compound (**9**). The reaction proceeds by an indole-2,3-quinodimethane which undergoes an intramolecular [4+2] cycloaddition to form the desired product. The sulfide is then oxidized to the sulfoxide with *m*-chloroperbenzoic acid, and cyclization of the five-membered ring is completed with trifluoroacetic anhydride. The sulfide is then removed with Raney nickel to give compound (**10**). Surprisingly, when compound (**10**) was treated with cyanogen chloride, chlorination occurred rather than the reagent functioning as a cyanating agent. It might also be noted that the amine protecting group was lost at this stage. Treating compound (**11**) with hydrochloric acid in methanol triggered the key rearrangement to the lactam (**12**) in 90% yield. Reduction to remove the lactam and subsequent oxidation to restore the carbonyl next to the indole nitrogen gave the eburnamonine (**1**).

The rearrangement that provides compound (**11**) is especially noteworthy, and the mechanism is shown in Scheme III. Protonation of the indole nitrogen cleaves the carbon-carbon bond at the 3-position of the indole to provide a

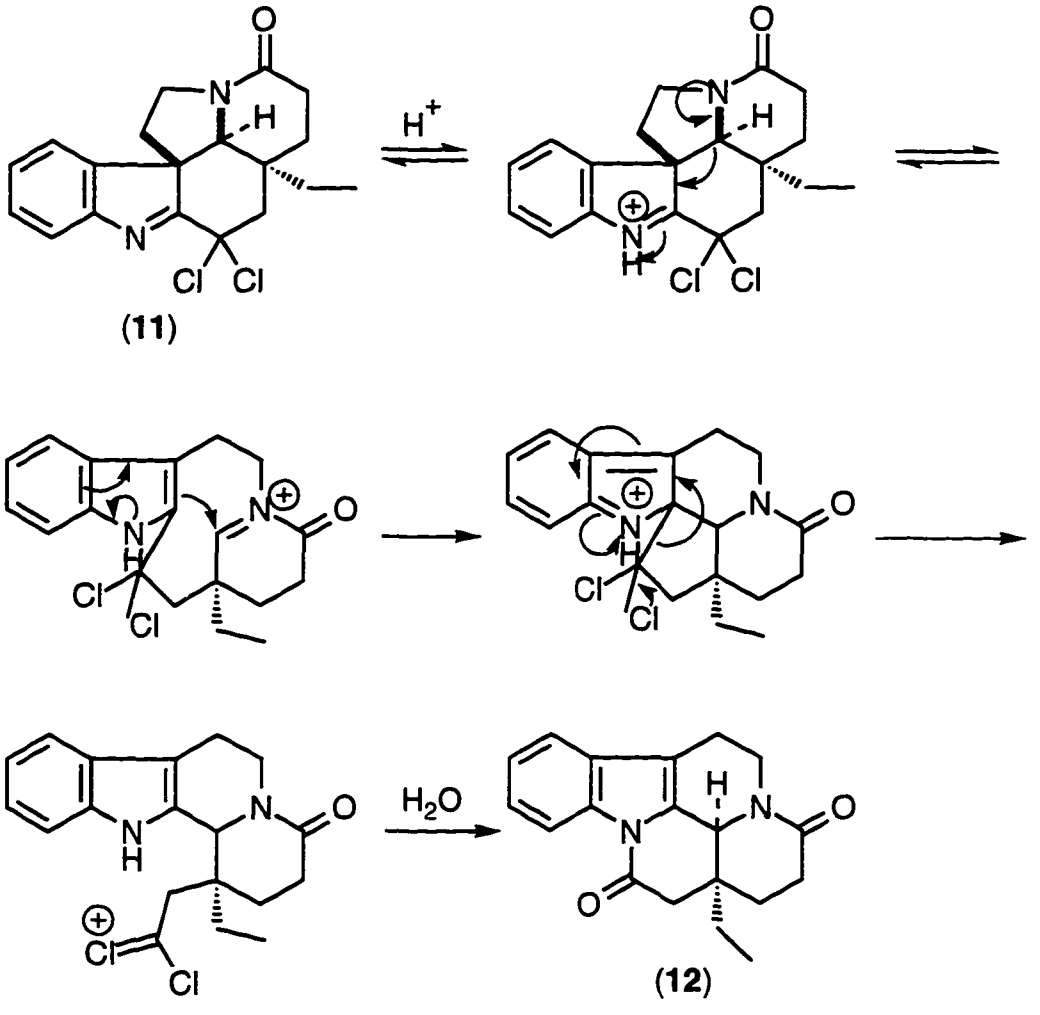
Scheme II


PhS
N
EtO
O
O
O
N
R
(R = -SO2C6H4OMe-p)
(7)
(8)
PhS
N
O
H
N
R
(9)


1) MCPBA
2) (CF3CO)2O
heat
3) Raney Ni
O
N
H
N
R
(10)
ClCN
O
N
H
N
Cl Cl
(11)


HCl
MeOH
H
N
N
O
O
(12)
1) LiAlH4
2) CrO3
pyridine
H
N
N
O
(1)

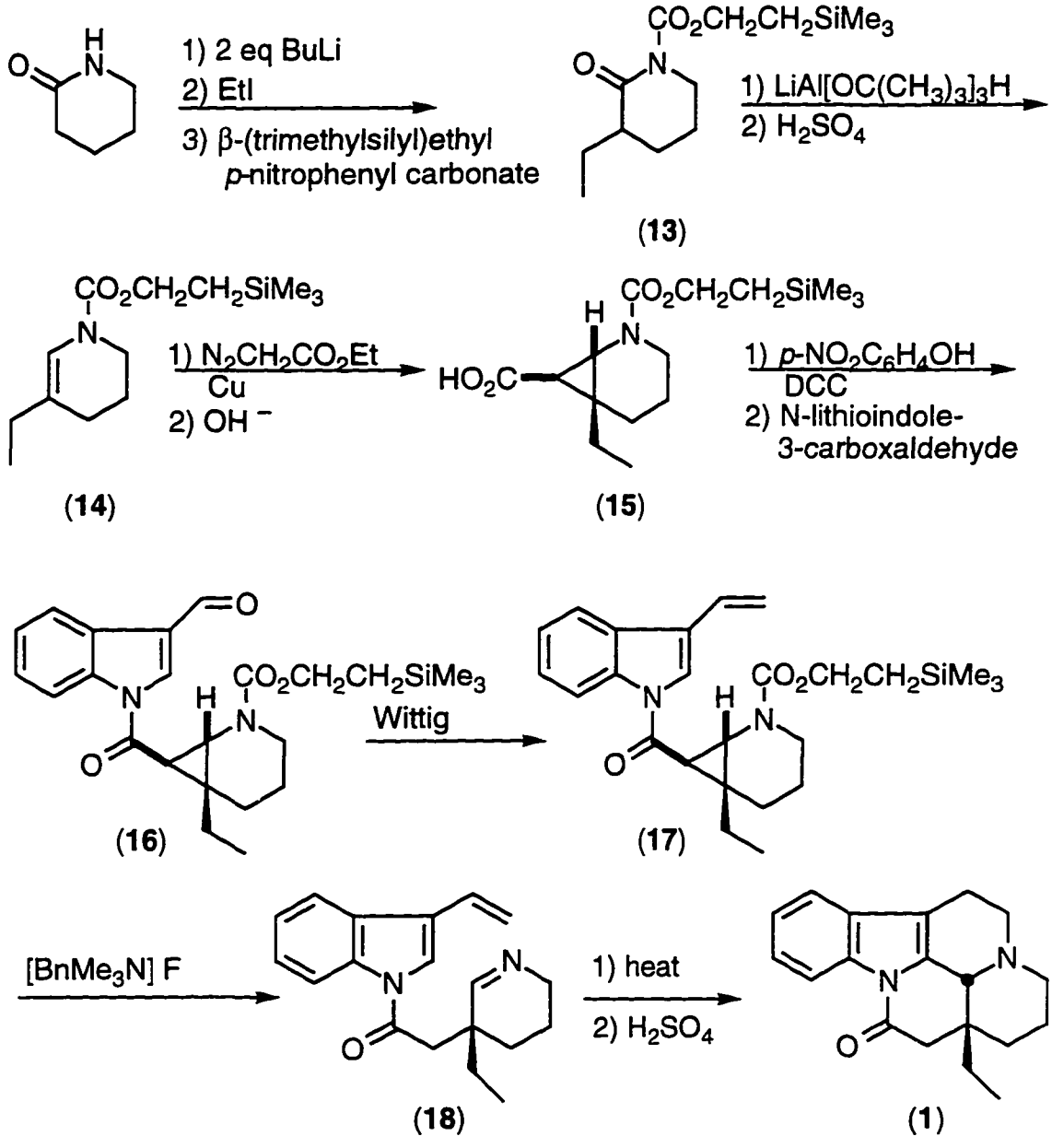
Scheme III



tetracyclic ring system. Reattachment at the 2-position restores the pentacyclic structure, which undergoes cleavage again to restore aromaticity. Nucleophilic attack by the indole nitrogen, followed by the addition of water, completes the mechanism to give compound (**12**).

The second synthesis which does not involve either a Pictet-Spengler or Bischler-Napieralski cyclization was completed in 1994 by Grieco and co-workers at Indiana University.[4a] Grieco's strategy (Scheme IV) involved the use of an intramolecular imino Diels-Alder reaction as the key step. Starting with the readily available valero lactam, Grieco and co-workers alkylated with ethyl iodide and protected the lactam nitrogen to give compound (**13**). This lactam was reduced

Scheme IV



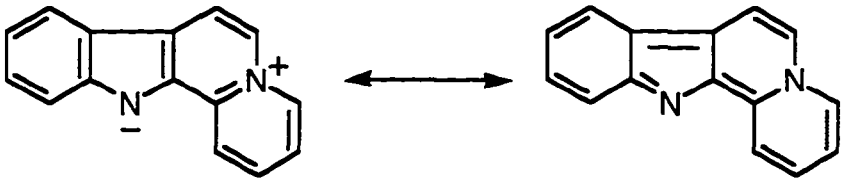
and acidified to give the eneamide (**14**). Treatment with ethyl diazoacetate and copper bronze provided a mixture of cyclopropane esters which could be epimerized to the desired stereoisomer. Saponification gave the corresponding acid (**15**). Coupling to the indole moiety was best achieved by converting the acid to the activated *p*-nitrophenyl ester and then treating with the lithiated indole to give compound (**16**). The desired vinyl indole was then prepared by subjecting the aldehyde to a Wittig reaction to provide compound (**17**). The amine protecting

group was removed by treatment with benzyltrimethylammonium fluoride, which also cleaved the cyclopropane ring to give the desired precursor (**18**) to the Diels-Alder reaction. Compound (**18**) smoothly underwent cyclization when heated, and subsequent isomerization provided eburnamonine (**1**).

History of Indolo[2,3-*a*]quinolizine Chemistry

The chemistry of zwitterionic indolo[2,3-*a*]quinolizine alkaloids has received little attention from synthetic chemists, and reviews of these types of compounds are scarce. However, recent studies indicate that some of these alkaloids exhibit antitumor activity, and interest in them has increased over the course of the past ten years, as evidenced by the review of Gribble.[6]

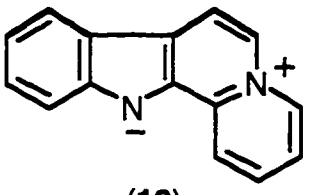
This ring system can be represented by two different resonance structures: the zwitterionic form **A** and the neutral form **B** without a charge. Support for this dual nature is given by the colored nature of the compounds, their high dipole moments, and their pH dependent ultraviolet-visible spectra. It might also be noted that these compounds may exist in the protonated form in plants, and in most cases, they are isolated and purified as their acid salts. Usually, the perchlorate ion is the counterion of choice, but examples of salts containing the chloride or bromide ion exist as well.[6]



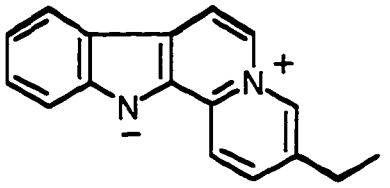
A **B**

Indolo[2,3-*a*]pyridocoline (**19**) can be regarded as the parent compound for a variety of indolo[2,3-*a*]quinolizine alkaloids. It has been isolated from the bark of *Gonioma kamassi* E. Mey (*Apocynaceae*).[7] Flavopereirine (**20**) is one of the most popular synthetic targets of this group of alkaloids and recently has drawn interest for its antitumor and antiviral activities, which also includes anti-HIV activity.[8] Flavopereirine (**20**) was isolated in the late 1950s by Janot[9] and co-workers, and

Rapoport[10] and co-workers almost simultaneously discovered it from the South American *Geissospermum laeve* (Vellozo). Schmid[11] and co-workers also isolated flavopereirine (**20**) from the South American *Strychnos melinoniana* Baillon (*Loganiaceae*).

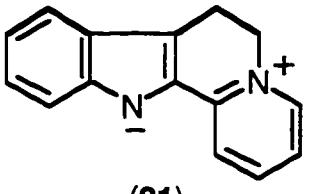


(**19**)

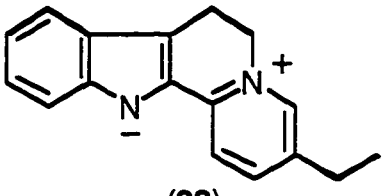


(**20**)

The 6,7-dihydro analogs [compounds (**21**) and (**22**)] of the indolo[2,3-*a*]quinolizine alkaloids have become relevant synthetic targets due to discoveries indicating that they have biological activity. 6,7-Dihydroflavopereirine (**22**) was isolated by Angenot and Denoël[12] from the Africa *Strychnos usambarensis* Gilg. (*Loganiaceae*). Recent discoveries show that 6,7-dihydroflavopereirine (**22**) has similar physiological activities as flavopereirine (**20**).[8,13] It might also be noted that when alkaloid numbering is used, these compounds are called 5,6-dihydroindolo[2,3-*a*]pyridocoline (**21**) and 5,6-dihydroflavopereirine (**22**). Both forms of numbering are used interchangeably in the literature.

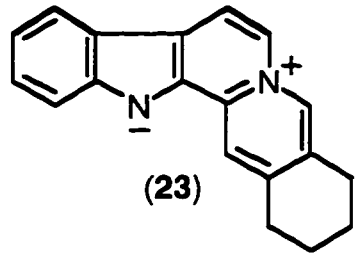


(**21**)



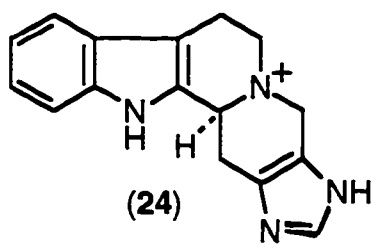
(**22**)

Of the pentacyclic indolo[2,3-*a*]quinolizine alkaloids, sempervirine (**23**) is probably the most common synthetic target. The first report of sempervirine (**23**) was by Janot and co-workers in 1948,[14] and shortly thereafter Woodward published its structure along with a synthesis of the *N*-methyl derivative.[15] Although it has been claimed that Woodward synthesized sempervirine (**23**),[16] no account of this has ever appeared in the literature. Within the last 15 years, sempervirine (**23**) has been identified as a selective destroyer of the proliferative capacity of cancer cells.[17]



(23)

Two pentacyclic indolo[2,3-*a*]quinolizine alkaloids that have been just recently discovered are Villagorgin A (**24**) and Villagorgin B (**25**). They were discovered in the gorgonian *Villagorgia rubra*, a genus that has never been studied before, in New Caledonia. Villagorgin A (**24**) was shown to produce strong inhibition on the acetylcholine induced contraction of guinea-pig ileum and showed an inhibitory effect against human platelet aggregation. These indole alkaloids are the only known alkaloids with an imidazole ring attached to the indoloquinolizidine skeleton.[18]



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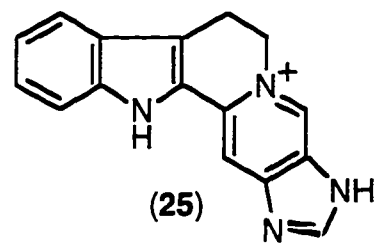
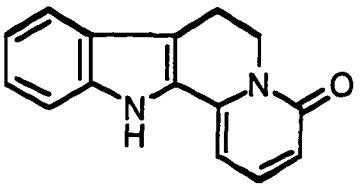


(25)

The last type of indolo[2,3-*a*]quinolizine structure that will be discussed is the 7,12-dihydroindolo[2,3-*a*]quinolizin-4(6*H*)-one structure, which has a lactam carbonyl placed on the D ring. The parent compound, 7,12-dihydroindolo[2,3-*a*]quinolizin-4(6*H*)-one (**26**) has been synthesized as an intermediate by two different groups but has not been isolated from natural sources.[19]

The 10-methoxy derivative is known more commonly as harmalanine (**27**). It is isolated from the seeds of *Peganum harmala* (*Zygophylaceae*), which is found on the Indo-Pakistan subcontinent and in other parts of Asia. The seeds are narcotic, anthelmintic, antispasmodic and used for asthma and cases of rheumatism. The alkaloids isolated from these seeds are also potent reversible inhibitors of monoamine oxidase, and in some cases, these compounds were found to have antimicrobial activity.[20]



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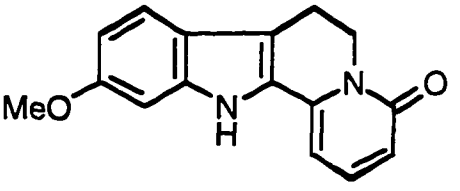
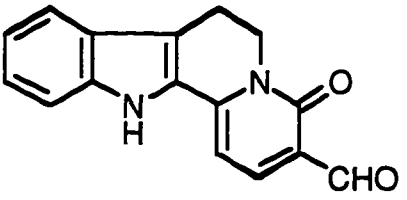


(27)



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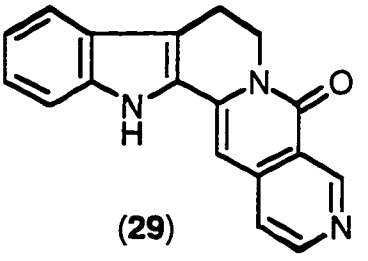


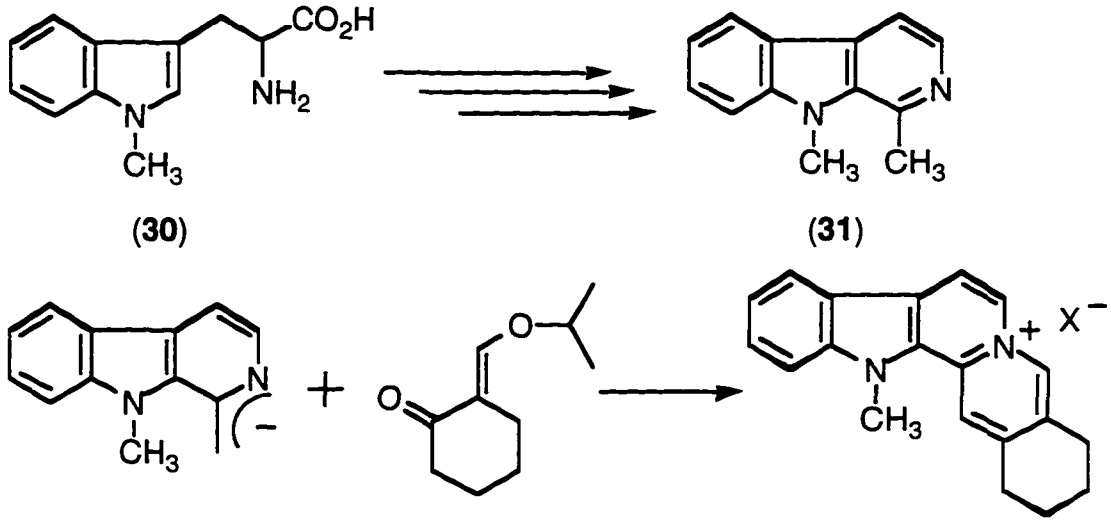
(29)

The other two alkaloids which are shown are nauclefidine (**28**) and nauclefine (**29**).[21] Nauclefidine (**28**) has been isolated from *Nauclea officinals.* The plant has been used as an antibacterial and anti-inflammatory agent by those who practice folk medicine in China. The structure was originally elucidated by researchers in China, who placed the formyl group in a position "para" to the lactam carbonyl.[22] That structure, however, was later revised by workers in Japan to the structure that is shown.[23]

Several syntheses of *indolo*[2,3-*a*]quinolizine alkaloids have been completed over the years, and they have been chronicled nicely by Gribble in 1988.[6] The earliest synthesis reported is of *N*-methylsempervirine by Woodward and co-workers in 1949.[15] Syntheses occurred periodically throughout the years, leading up to the most recent synthesis of flavopereirine (**20**) and 5,6-dihydroflavopereirine (**22**) by Lounasmaa and co-workers in 1996.[24]

The synthesis of *N*-methylsempervirine (**34**) by Woodward (Scheme V) was very direct. The synthesis was started with *N*-methyltryptophan (**30**) and used known literature procedures to obtain *N*-methylharman (**31**).[25] This known compound was then lithiated and treated with the corresponding cyclohexanone (**33**) to give the desired *N*-methylsempervirine (**34**).

Scheme V



(30) (31)

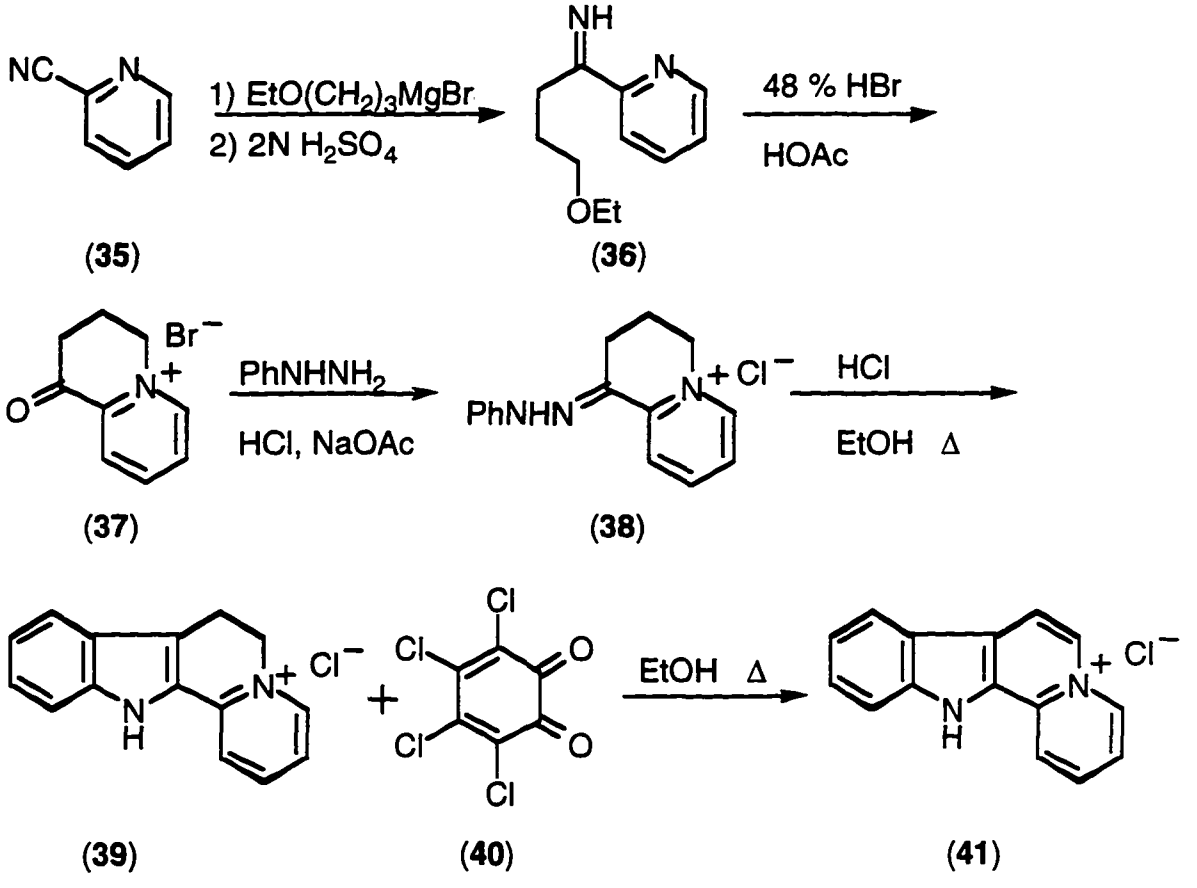
(32) (33) (34)

In the late 1950's, two groups used very similar routes to synthesize the salt of indolo[2,3-*a*]quinolizine (**41**). Glover and Jones were the first chemists to use a Fischer indole synthesis to make an indolo[2,3-*a*]quinolizine.[26] They were followed shortly thereafter by Swan and co-workers, who published almost an identical synthesis.[27]

The Swan synthesis is shown in Scheme VI. Starting with 2-cyanopyridine (**35**) and 3-ethoxypropylmagnesium bromide, they were able to isolate the imine (**36**). Treating the imine with concentrated hydrobromic acid and acetic acid cyclized the product to the ketone (**37**) in 68 % yield. Compound (**37**) was then converted to the corresponding hydrazone (**38**) in 57 % yield, which then underwent the Fischer-indole reaction to give compound (**39**) in 57 % yield. *Ortho*-chloranil (**40**) was then used to convert the 6,7-dihydro salt to the desired compound (**41**) in 47 % yield. Swan then applied this same route to synthesize flavopereirine (**20**) and sempervirine (**23**).

In 1963 Potts and co-workers used what is probably the most common strategy for making indolo[2,3-*a*]quinolizine alkaloids, in their efforts to make flavopereirine (**20**) and sempervirine (**23**).[28] In this strategy, a 3-substituted indole

Scheme VI

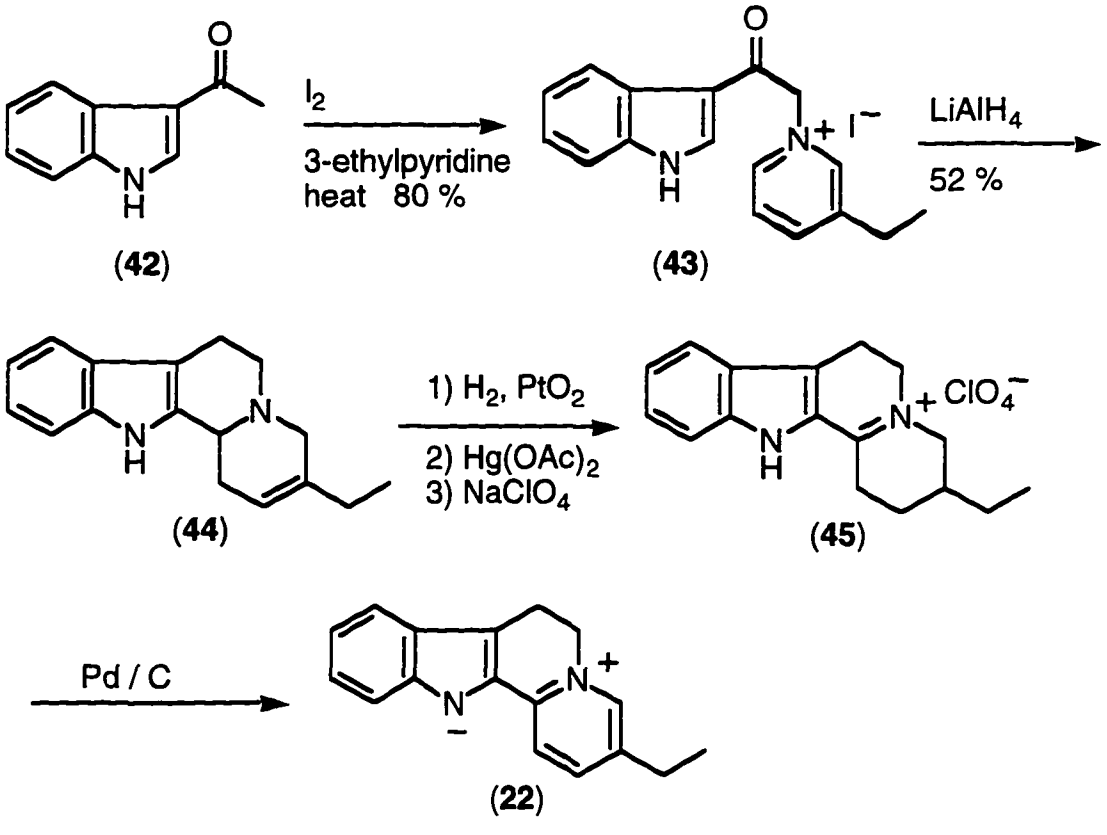


is combined with an appropriately substituted pyridine to form a pyridinium salt. The salt is then further manipulated to give the desired indoloquinolizine.

In Potts' synthesis of flavopereirine (**20**) (Scheme VII), he starts with 3-acetylindole (**42**) and heats it in the presence of iodine and 3-ethylpyridine to give the corresponding pyridinium salt (**43**) in 80 % yield. Lithium aluminum hydride reduction not only reduced the ketone, but it reduced and cyclized the pyridine ring as well, giving compound (**44**) in 52 % yield. The tetrahydro compound (**44**) was then put through a cycle of reduction and oxidation to give compound (**45**) as its perchlorate salt, which was treated with palladium on carbon to give the desired molecule (**22**).

In 1988 Gribble and co-workers devised a clever plan to directly synthesize the indolo[2,3-*a*]quinolizine ring system.[29] Basing his plan upon the ready availability of 2-(2-pyridinyl)indoles, he planned to use the nitrogen of the pyridine

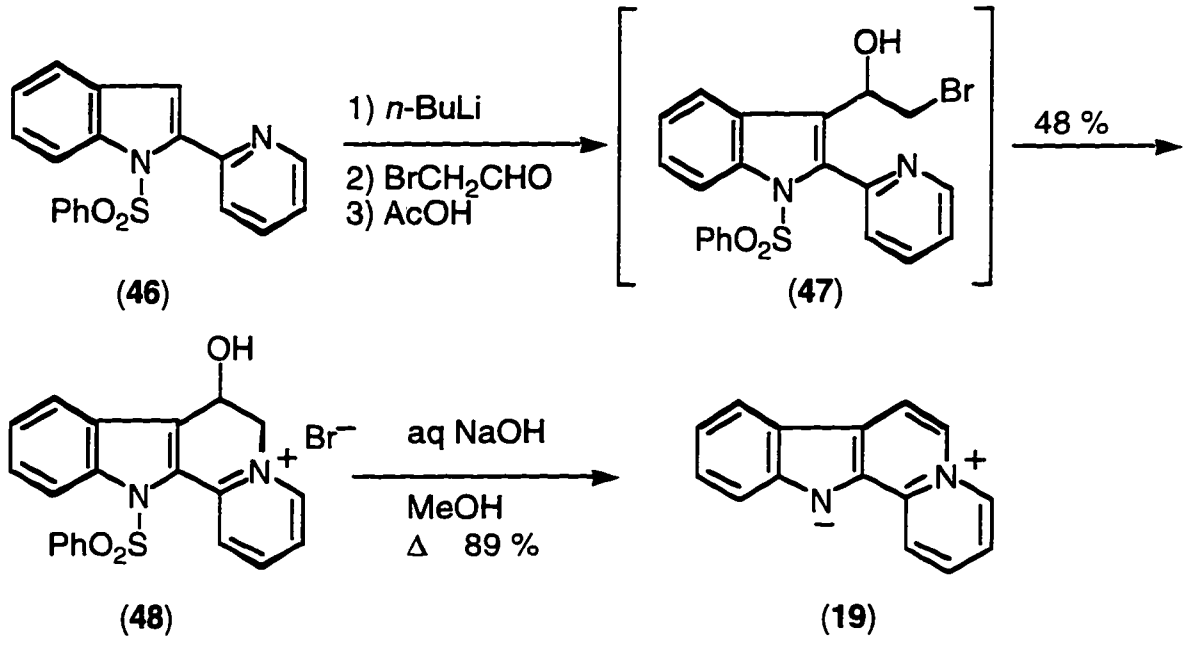
Scheme VII



ring to help direct metallation at the 3-position of the indole. First, he had to choose a protecting group for the indole nitrogen. This group needed to be easily removable since earlier work by Stevens had shown that some protecting groups, such as the benzyl group, were difficult to remove.[30] Gribble chose the *N*-phenylsulfonyl protecting group. Starting with compound (**46**) in Scheme VIII, he was able to lithiate at the 3-position of the indole by treating with *n*-BuLi. This nucleophile was then quenched with 2-bromoacetaldehyde to afford intermediate (**47**), which cyclized upon workup to give the pyridinium salt (**48**) in 48 % overall yield. Treatment with base deprotected the *N*-phenylsulfonyl protecting group, as well as eliminating the alcohol, to give the desired product (**19**) in 89 % yield.

The last synthesis that will be discussed was done in 1995 by Fürstner and co-workers at the Max-Planck-Institut für Kohlenforschung in Germany.[21] This synthesis makes use of a low-valent titanium induced reductive coupling to form

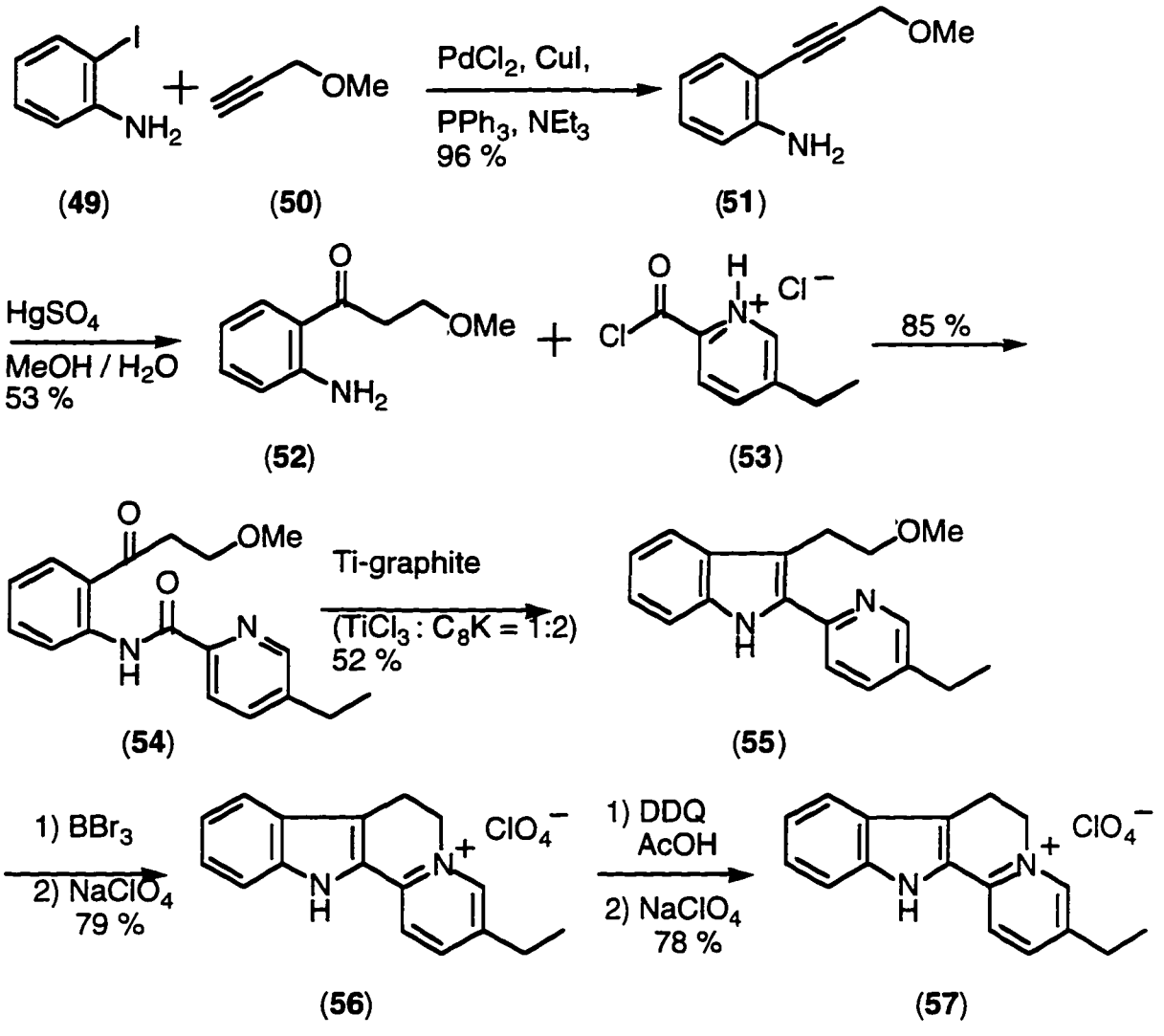
Scheme VIII



(46) (47) (48) (19)

the five-membered ring of the indole. Starting with 2-iodoaniline (**49**) (Scheme IX), Fürstner used a palladium-catalyzed coupling reaction to form the desired aniline (**51**) in excellent yield. The alkyne was then treated with mercuric sulfate in aqueous methanol to provide the desired ketone (**52**) in 53 % yield. This aniline was then coupled with the acid chloride (**53**) to give the corresponding amide (**54**) in a rather good 85 % yield. Refluxing compound (**54**) in a suspension of titanium-graphite in THF gave the desired indole (**55**) in modest yield. Cyclization of the C ring was then achieved by treating the methyl ether with boron tribromide and isolating the compound as its perchlorate salt (**56**) in 79 % yield. Treating the dihydro compound with DDQ afforded the desired compound (**57**), which was once again isolated as its perchlorate salt.

Scheme IX



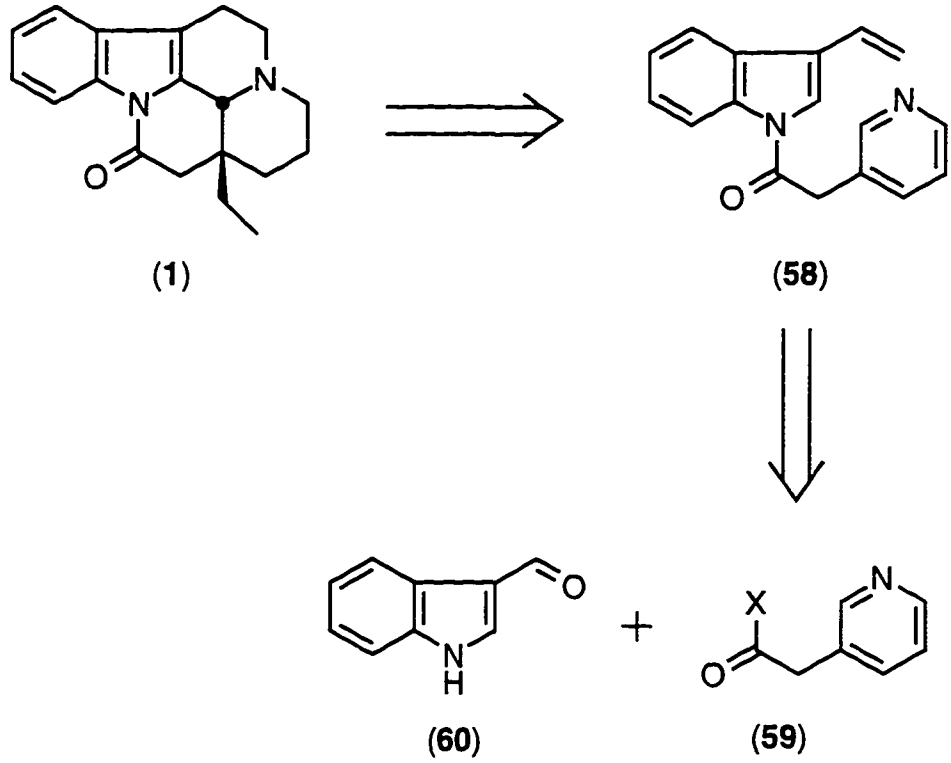
(49) (50) (51) (52) (53) (54) (55) (56) (57)

Results and Discussion

We became interested in developing a synthetic route to eburnamonine (**1**) because of its intriguing chemical structure and interesting biological activity. At the time we started the project, we were amazed that almost all of the known syntheses followed the same type of route via a Pictet-Spengler or Bischler-Napieralski cyclization. We were also surprised that no one at that time had tried a route that contained a Diels-Alder cycloaddition as its key reaction. Our original strategy was based on this observation.

Our original strategy is shown in the retrosynthetic analysis shown in Scheme X. We had hoped that the pentacyclic framework of eburnamonine (**1**) could be constructed from an intramolecular [4+2] cycloaddition of a molecule such as (**58**). A molecule such as (**58**) could easily be assembled from precursors such as the appropriately substituted 3-pyridyl acetic acid derivative (**59**) and indole-3-carboxaldehyde (**60**).

Scheme X



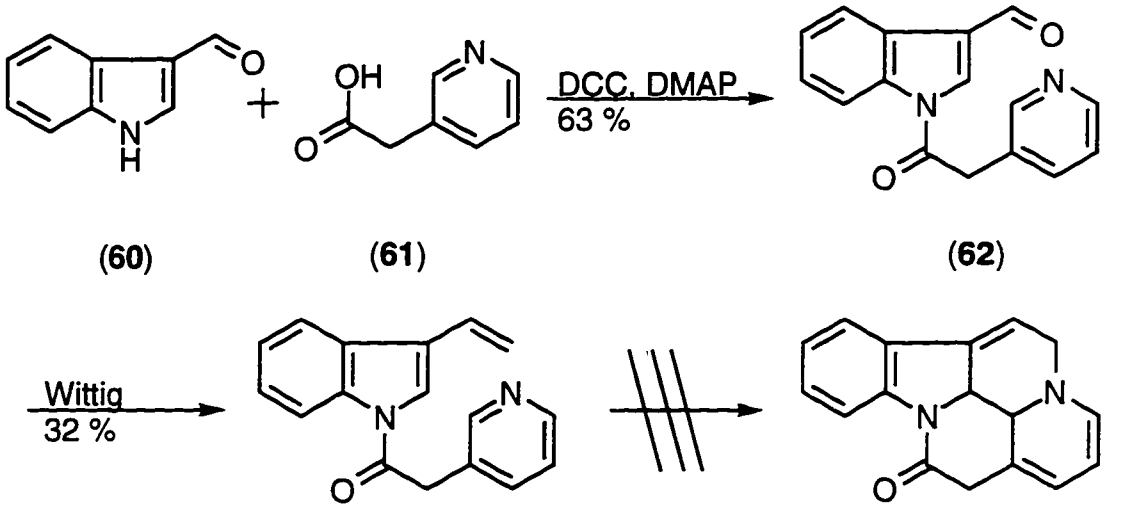
(**1**) (**58**)

(**60**) (**59**)

We began our synthesis (Scheme XI) by using 1,3-dicyclohexylcarbodiimide (DCC) and a catalytic amount of 4-dimethylaminopyridine (DMAP) to couple indole-3-carboxaldehyde (**60**) and the readily available 3-pyridyl acetic acid (**61**) in a 63 % overall yield. Many experimental conditions were tried before settling on the DCC coupling reaction. Included were attempts at coupling the corresponding acid halide with the indole (**60**), and attempts involving the analogous carbonate of acid (**61**). However, all these attempts led to little or no coupling product. With compound (**62**) in hand, we then converted the aldehyde to the corresponding

alkene (**58**) via a Wittig reaction. We were now ready to try our key Diels-Alder reaction. Unfortunately, subjecting compound (**58**) to high temperatures did not lead to any cyclized product (**63**). We also tried to promote the reaction with Lewis acid catalysts, but once again, we met with failure. Around this same time, Grieco and co-workers published their synthesis of eburnamonine (**1**) using a Diels-Alder approach,[4a] and we decided to seek an alternative route.

Scheme XI

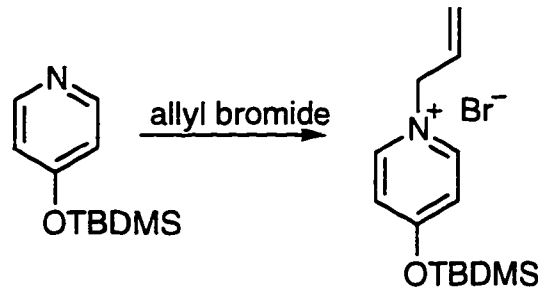


(**60**) (**61**) (**62**)

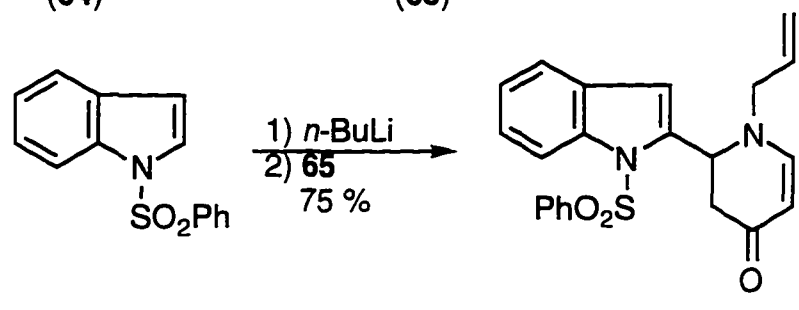
(**58**) (**63**)

The next method that we tried was to alkylate a pyridinium salt with a *N*-protected indole anion. We first made the pyridinium salt (**65**) by reacting the corresponding pyridine (**64**) with allyl bromide (Scheme XII). The oxygen functionality at the 4-position of the pyridine ring would eventually have to be removed for the completion of eburnamonine (**1**), but we needed it to block "para" attack by the nucleophile. The oxygen functionality could have also been used later on in the synthesis to promote cyclization of the lactam ring of eburnamonine (**1**). The allyl group would be eventually contracted by one carbon and connected to the 3-position of the indole. Treating the pyridinium salt (**65**) with the lithiated indole (**66**) provided compound (**67**) in 75 % yield. Unfortunately, we were unable to manipulate the allyl group any further and this route had to be modified.

Scheme XII

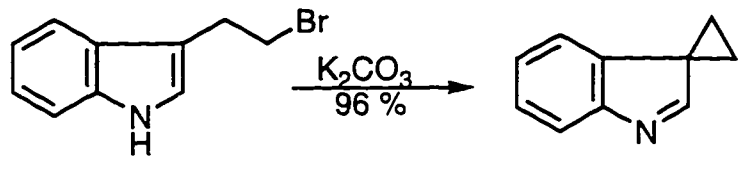


(**64**) (**65**)



(**66**) (**67**)

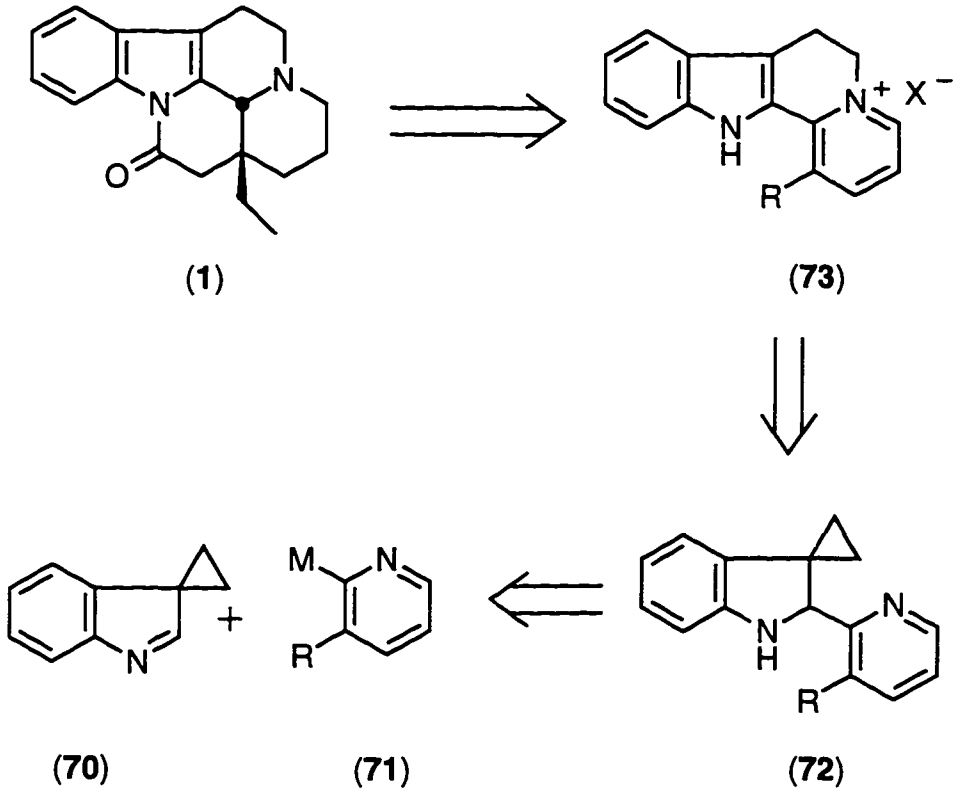
We planned to modify our synthesis by using 3-(2-bromoethyl)indole to *N*-alkylate the pyridine ring and then cyclize the ring in an intramolecular fashion. During one of the experiments towards this route, we made an interesting discovery. Treating the 3-(2-bromoethyl)indole (**69**) with base provided us with the spiro compound (**70**). Upon searching the literature, we found that this molecule had already been reported by Rapoport and co-workers.[31] Rapoport, however, did not do any chemistry with compound (**70**).



(**69**) (**70**)

Surprisingly, alkylating the 2-position with a pyridine anion equivalent does not appear to have been reported. Therefore, we decided to redirect our efforts toward this pathway. Our next strategy towards eburnamonine (**1**) (Scheme XIII) was to take the spiro compound (**70**), and alkylate it with the appropriately

Scheme XIII



(**1**) (**73**)

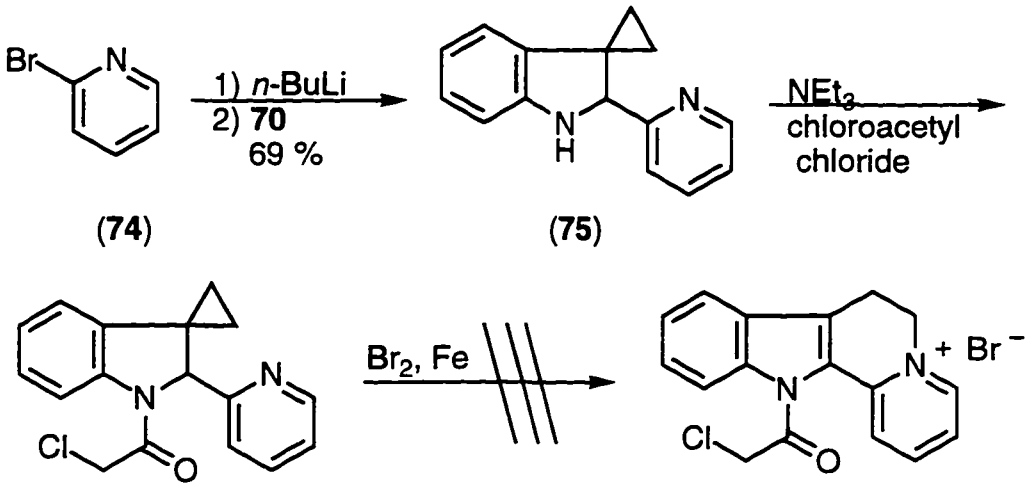
(**70**) (**71**) (**72**)

substituted pyridine (**71**). The cyclopropane ring would then be opened and connected to the nitrogen of the pyridine ring to form an intermediate such as (**73**). Reduction of the pyridine and cyclization would then lead to the desired product (**1**).

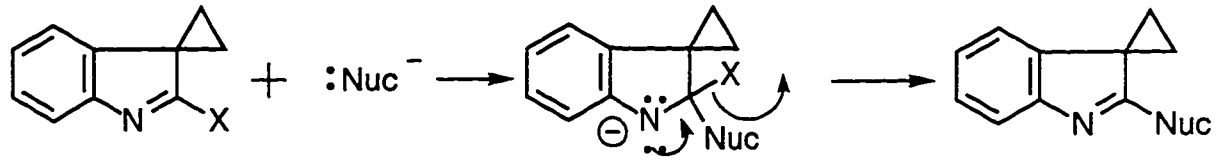
The first step of the synthesis was the addition of the metallated pyridine to the imine (**70**) (Scheme XIV). Starting with the readily available 2-bromopyridine (**74**), we made the corresponding anion at the 2-position by treatment at -78 °C with *n*-BuLi. Adding this anion to the imine (**70**) provided us with the 1,2-addition

product (**75**) in 69 % percent yield. We next installed the carbonyl functionality on the indole nitrogen by treating compound (**75**) with chloroacetyl chloride and triethylamine to give the amide (**76**). Unfortunately, our attempts to open up the cyclopropane ring met with failure.[32]

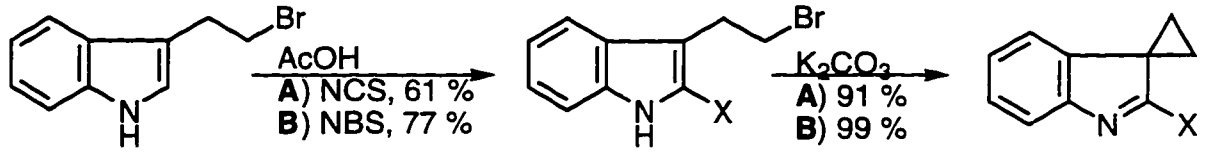
Scheme XIV



Because we were unable to open the cyclopropane of the indoline structure, we hoped that by changing the indoline amine to an imine, we would then be able to somehow open up the cyclopropane ring. Our first idea was to design a molecule such as the imine (**78**), where addition of a nucleophile would cause loss of the X group and regenerate the imine moiety.



The first compound that we set out to make was the imine where X = Cl. Starting with 3-(2-bromoethyl)indole (**69**), we were able to generate the indole (**81**) with the chlorine at the 2-position by treating with *N*-chlorosuccinimide (NCS) in acetic acid. Treating this indole (**81**) with base provided us with the desired imine (**82**) in 91 % yield. We were also able to use similar conditions so that X = Br, providing us with compounds (**83**) and (**84**).

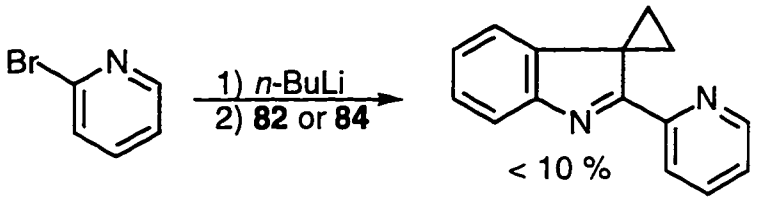


(**69**)

(**81**) X = Cl
(**83**) X = Br

(**82**) X = Cl
(**84**) X = Br

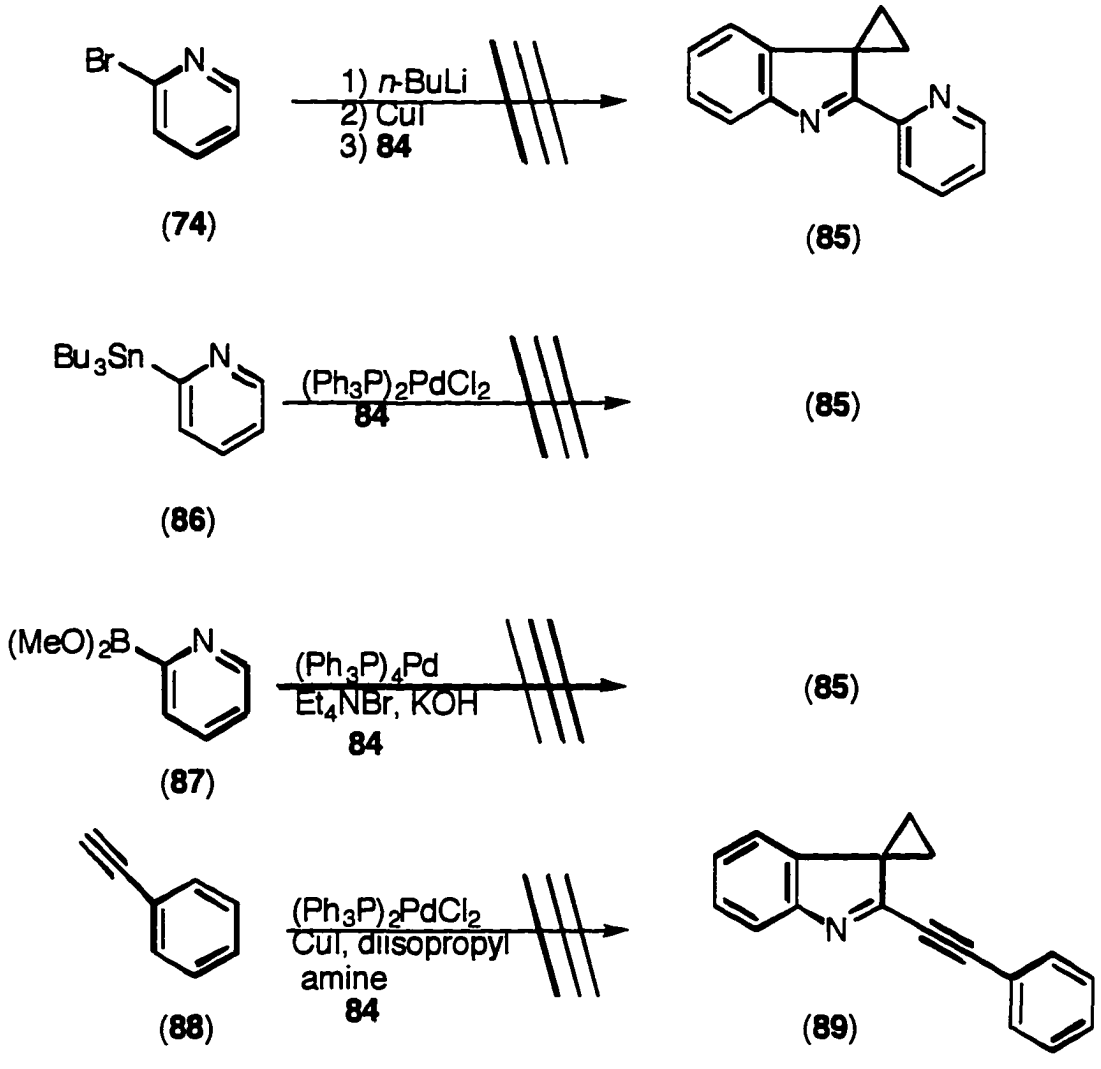
Once again we made the 2-lithio pyridine from its bromide counterpart (**74**) and reacted it with the imine (**82**). We were able to isolate some of the desired compound (**85**) after column chromatography, but the yield (< 10 %) was too low to be of any synthetic value. We tried again with the bromoimine (**84**), but we met the same fate. Part of the problem was that the reaction did not go to completion, leaving a mixture of starting material and products. Normally, this is not a problem as reaction mixtures can be cleaned up via silica gel chromatography. However, the compound (**85**) was too sensitive and could not be purified by column chromatography.



(**74**)

(**85**)

Scheme XV

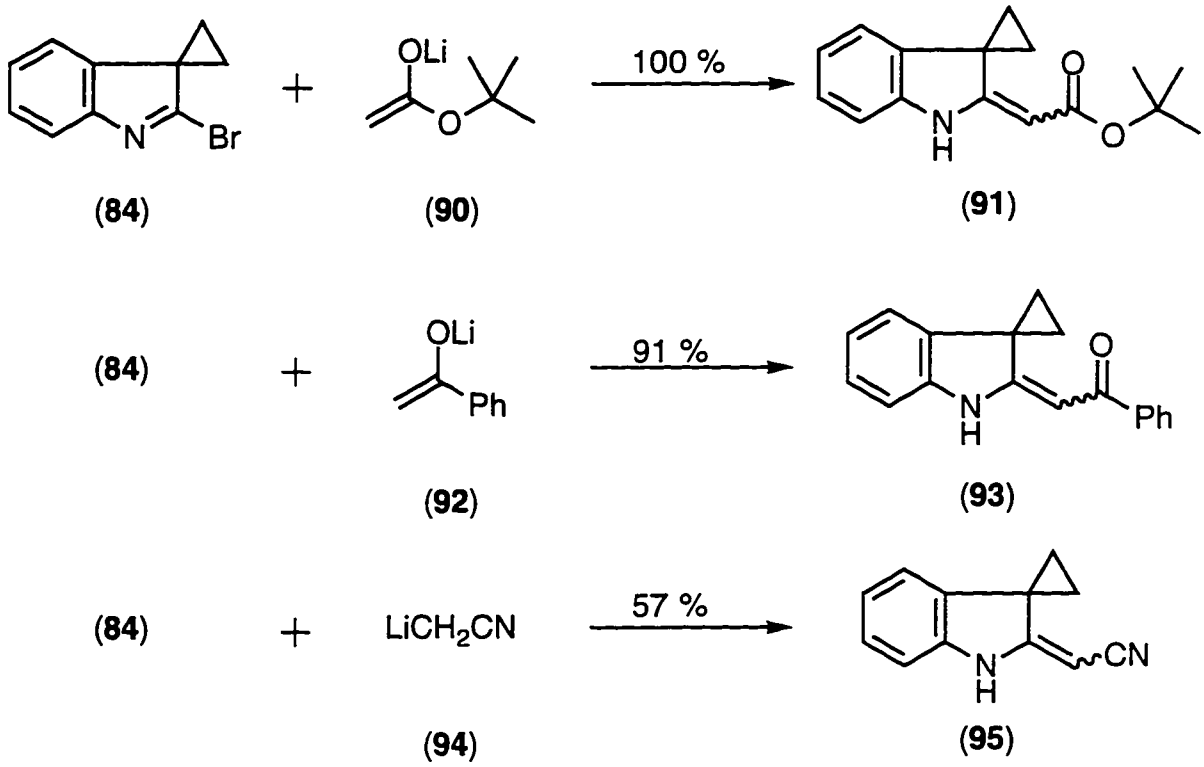


To correct this problem, we realized that compound (**8 5**) had to be generated completely and cleanly if we wanted to use this pathway. Therefore, we began trying to couple the imines (**8 2**) and (**8 4**) with different types of organometallics (Scheme XV). The first metal that we tried was copper, and that reaction did not work. We then tried coupling the vinyl bromide (**8 4**) with organotin[33] reagents (**8 6**) via Stille coupling,[34] but this did not result in any of the desired product. We also tried to couple (**8 4**) with pyridineboronic acids (**8 7**) by using the conditions of Suzuki,[35] but once again we met with failure. We also tried to couple acetylenes to the vinyl bromide (**8 4**) using the conditions of

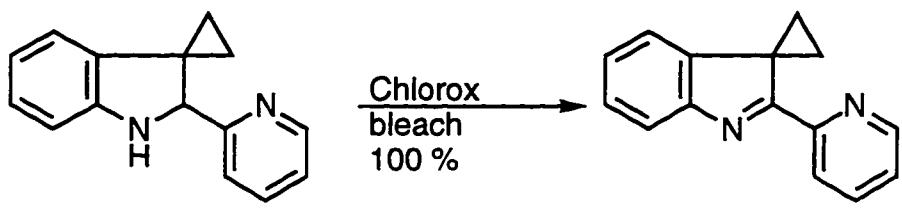
Sonogashira[36] in hopes that we could further manipulate such a molecule (**89**) into our desired product, but these conditions did not work either.

At this point we wanted to verify that our assumption that the low yield of compound (**85**) was due in fact to it being sensitive to the silica gel and not the reaction conditions. To do this, we decided to react imine (**84**) with a variety of nucleophiles to see what kind of yields we would get (Scheme XVI). Treating *tert*-butyl acetate with lithium diisopropylamide provided the anion (**90**), which reacted nicely with compound (**84**) to provide compound (**91**) in quantitative yield. The lithium anion of acetophenone (**92**) also reacted well, giving compound (**93**) in excellent yield. Finally, the lithium anion of acetonitrile (**94**) was treated with the imine (**84**), and it gave 57 % yield of compound (**95**). Unfortunately, more hindered anions, such as the anion of 3-pentanone, could not be added to (**84**).

Scheme XVI



With these results we were convinced that we had a good general pathway to a variety of natural products, including eburnamonine (**1**), if we could find a way to open the cyclopropane ring. Therefore, we retraced our steps and returned to compound (**75**). We began to look at oxidation of the indoline amine to an imine and then proceed via that pathway. We first tried to use *tert*-butyl hypochlorite[37] and calcium hypochlorite as oxidizing reagents, but to no avail. Finally, we were able to achieve oxidation with Chlorox bleach to get our desired compound (**85**) in quantitative yield.[38] Unfortunately, the imine (**85**) was sparingly soluble in most organic solvents, and this fact made further work on this compound somewhat problematic.

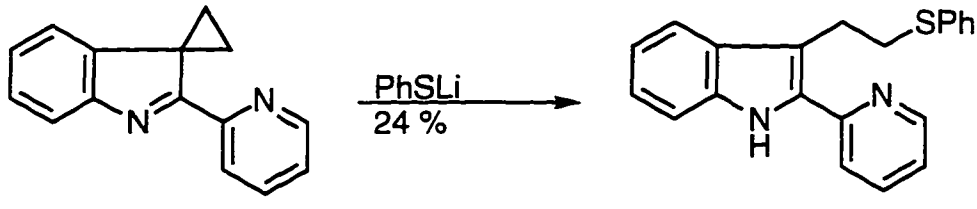


(**75**) (**85**)

With a reproducible pathway to compound (**85**), we next set out to open the cyclopropane ring and cyclize the pyridine ring onto the newly-formed ethyl appendage. We had hoped that Lewis acid coordination to the indole nitrogen would open the cyclopropane ring, and the resulting carbocation would be trapped by the pyridine nitrogen. We tried a host of reagents (HBr; $TiCl_4$; $BF_3 \cdot OEt_2$, NaI; $SnCl_4$; KBr, $ZnBr_2$, crown ether) that had been used successfully by others.[39] However, in our hands, these reactions failed to work and destroyed the starting material.

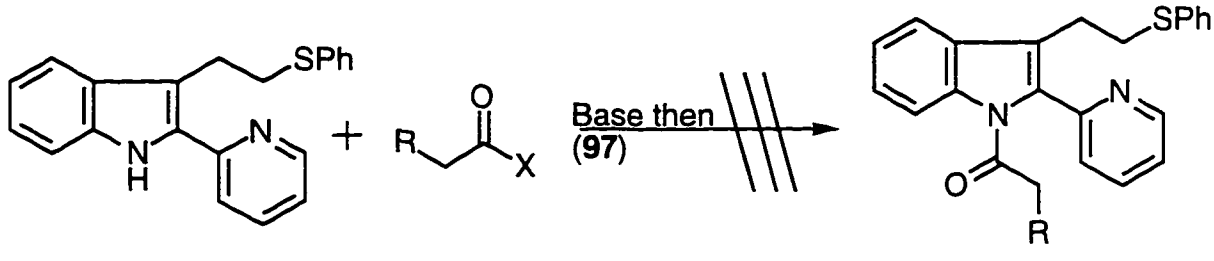
Being that all the reaction conditions that we tried had been acidic conditions, we then began to look at ways of opening the cyclopropane ring under basic conditions. We thought that if we could possibly add a nucleophile via 1,4-addition and then convert this nucleophile to a leaving group, then we would have a viable pathway to the eburnamonine (**1**) ring system. We began to look at sulfur

compounds because of their nucleophilicity and ability to be converted to other functional groups. We were pleased to learn that treatment of compound (**85**) with the lithium anion of thiophenol produced the 1,4-addition product (**96**) in 24 % purified yield. We were naturally disappointed with the low yield, but we felt that this was mainly due to the insolubility of compound (**85**). The results look much better if one considers that the overall yield of the preceding two steps [from compound (**75**)] is 24 % or approximately 50 % for each step.



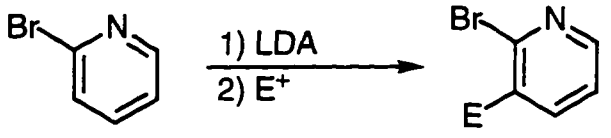
(**85**) (**96**)

Now that we had a method for opening the cyclopropane ring, we wanted to find a method for installing the carbonyl next to the indole nitrogen. Unfortunately, this process proved tougher than we anticipated. Treatment of the compound (**96**) with a variety of bases (triethylamine, lithium diisopropylamide, *n*-butyl lithium) and quenching with acid chlorides or anhydrides (**97**) did not lead to any of the desired product (**98**). In most cases, just starting material was recovered.



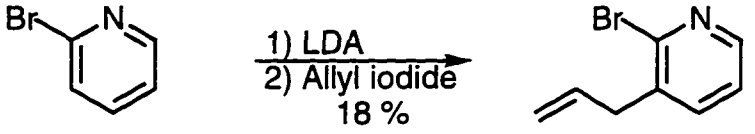
(**96**) (**97**) (**98**)

About this time, an article appeared in the literature in which 2-bromopyridine (**74**) was selectively lithiated at the 3-position.[40] Quenching this compound with an electrophile produced the 3-substituted 2-bromo pyridine (**99**) in moderate yield (57 %).



(**74**) (**99**)

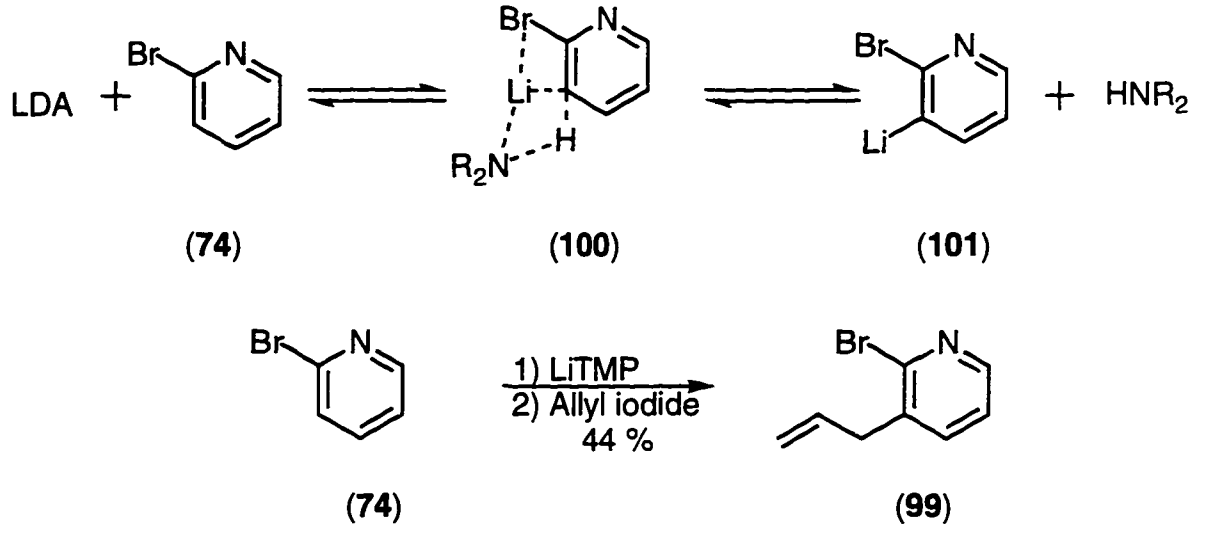
We then decided to change our plan of attack by using this developed chemistry and substituting the pyridine ring before attaching it to the indole moiety. The appendage that we decided to attach was the allyl group because allyl iodide is a good electrophile and the double bond could eventually be manipulated into a carbonyl via ozonolysis. However, we were disappointed upon doing the reaction that we only obtained a 18 % overall yield of the desired 3-substituted pyridine (**99**).



(**74**) (**99**)

Going back to the original reference,[41] we discovered that the original authors claimed that removal of the proton at the 3-position was an equilibrium process (Scheme XVII). We then reasoned that if we used a stronger hindered base, then the equilibrium would be shifted further to the right and give a higher yield. The base that we chose was lithium 2,2,6,6-tetramethylpiperidine (LiTMP), and we were happy to discover that changing bases improved the yield of the reaction from 18 % to 44 %.

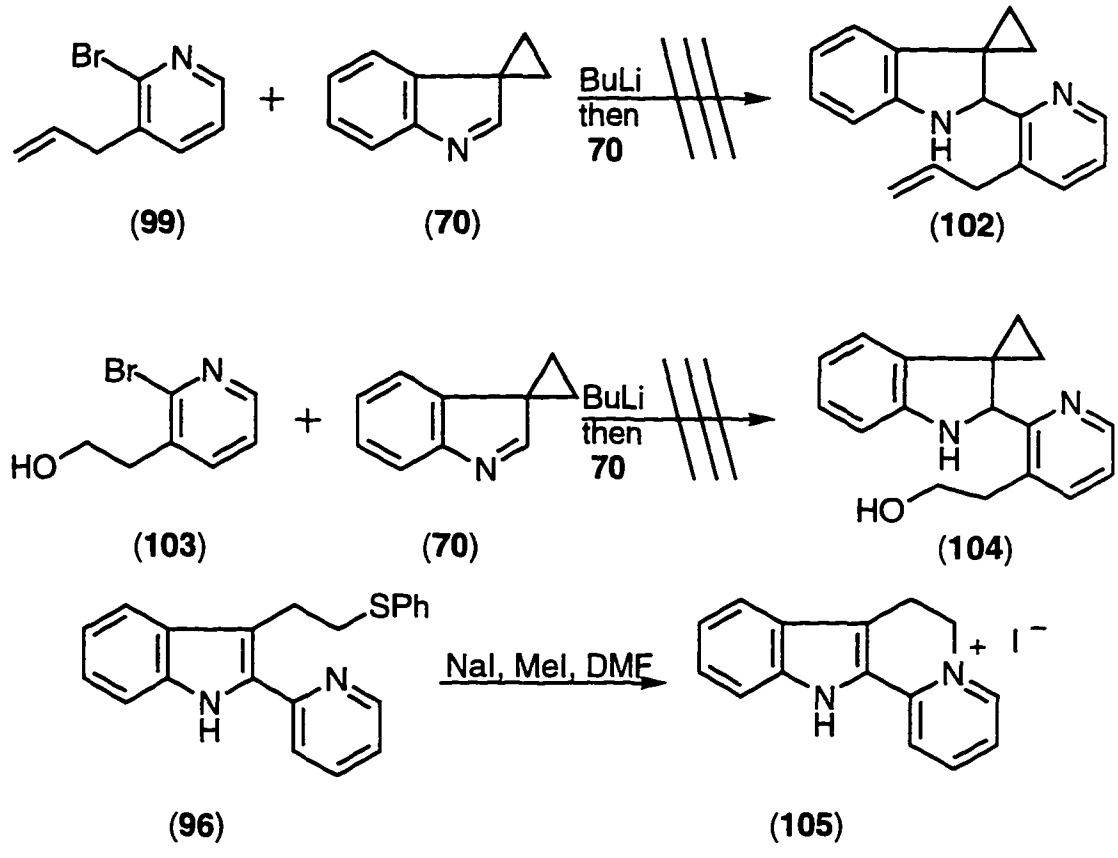
Scheme XVII



With compound (**99**) in hand, we were now ready to continue our synthesis of eburnamonine (**1**). Unfortunately, upon metallating compound (**99**) with *n*-BuLi and quenching with imine (**70**) (Scheme XVIII), we were unable to isolate any of the 1,2-addition product (**102**). We then tried to manipulate the allyl side chain, converting it to a 2-hydroxyethyl substituent. However, upon trying the reaction with this analog (**103**), we were still unable to isolate any of the desired addition product (**104**). It appears that the electrophile (**70**) will only react with relatively unhindered nucleophiles as we had trouble before when the nucleophile became somewhat bulky.

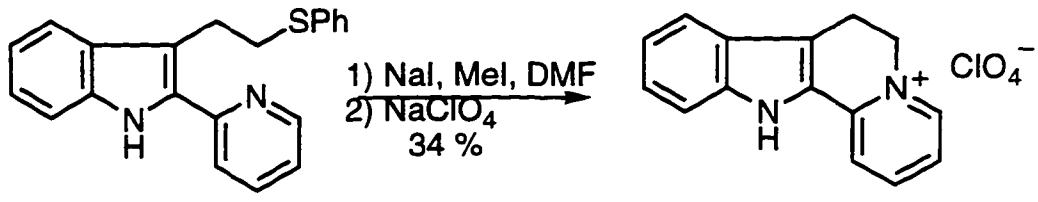
With the aforementioned discouraging results, we decided to go back to compound (**96**) and work on closing the C ring. Earlier, we had tried to change the phenylsulfide group in compound (**96**) to an iodide. Naturally, we then expected the iodide to be displaced by the nitrogen on the pyridine ring to give us the desired cyclized product (**105**). Using a method developed by Corey,[42] we treated compound (**96**) with excess sodium iodide and methyl iodide. At the time, we felt that we had made the desired compound (**105**), but unfortunately the compound was too insoluble for complete NMR characterization. The only encouraging sign

Scheme XVIII



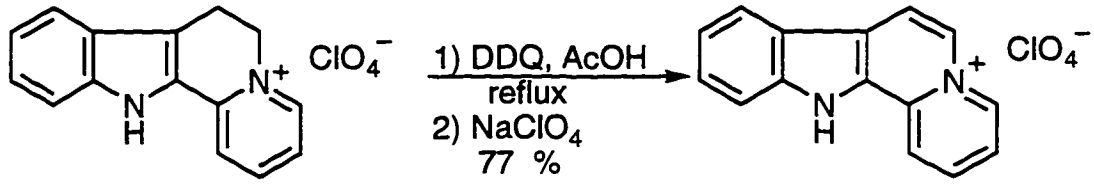
that the reaction was working was that thioanisole was being isolated from the reaction mixture.

Upon searching the literature for compounds of this type, we realized that we had stumbled upon a relatively uncharted area of research so we began to redirect our efforts towards the synthesis of indolo[2,3-*a*]quinolizines. In addition to these molecules being unstudied, the potent biological activity[6] made them an even more attractive synthetic target. Taking our cues from the literature,[21] we tried isolating the indolo[2,3-*a*]quinolizines as their perchlorate salts rather than the iodide salt. This change immediately provided dividends as the reaction of compound (**96**) with sodium iodide and methyl iodide was repeated. This time, however, the reaction mixture was treated with sodium perchlorate to afford compound (**106**) in 34 % yield.



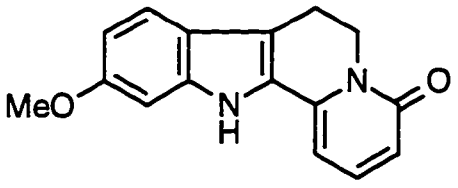
(**96**) (**106**)

Compound (**106**) was just one step away from the natural product indolo[2,3-*a*]pyridocoline (**19**). So using known conditions,[21] we treated compound (**106**) with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) in refluxing acetic acid, and we isolated the desired product as its perchlorate salt (**107**) in 77 % yield.



(**106**) (**107**)

At this point, we wanted to show that the pathway which we had developed was general and could be used for a wide variety of natural products. The first two natural products that came to mind were harmalanine (**27**) and nauclefidine (**28**). To design a pathway to these molecules, we had to install an oxygen functionality next to the pyridine nitrogen. We did this by starting with the known 2-bromo-6-methoxypyridine[43] (**108**) (Scheme XIX, page 33). Treating this compound with *n*-BuLi and quenching the resultant anion with the imine (**70**), we were able to isolate compound (**109**) in 73 % yield.



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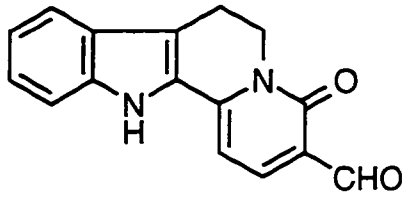
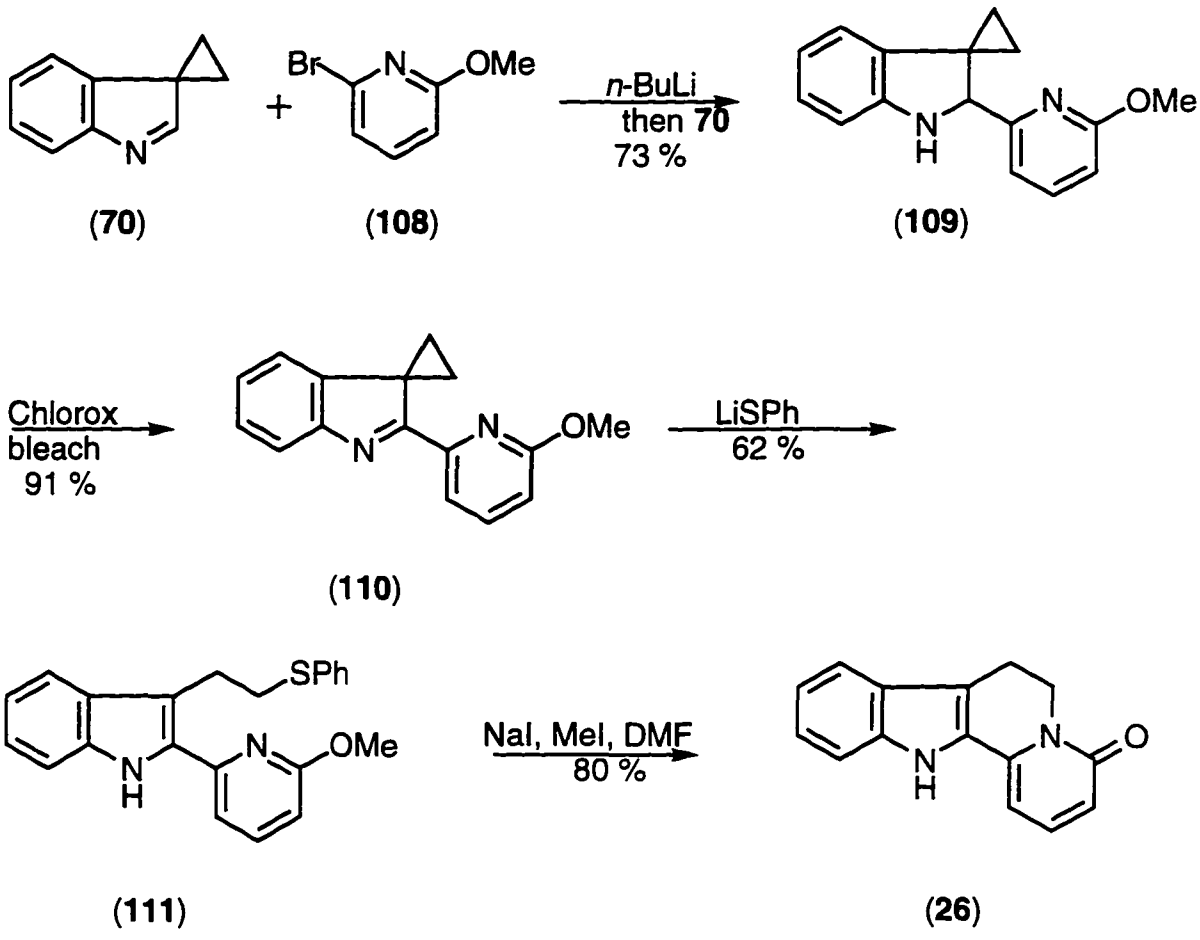


(28)

It might also be mentioned at this time that we made an important discovery about the purification of these types of molecules. Previous attempts at purification by silica gel chromatography led to severely reduced yields and the compounds were still relatively impure. However, if the compounds were subjected to chromatography on neutral alumina with deoxygenated solvents, good yields of pure compounds could be obtained.

Treating the indoline (**109**) with bleach provided the imine (**110**) in 91 % yield. The cyclopropane ring of this imine (**110**) was then opened via 1,4-addition with lithium thiophenoxide to give compound (**111**) in 61 % yield. This yield is rather significant, because in the series where no methoxy group was present on the pyridine ring, only a 24 % yield was obtained from this same reaction. Much of the difference in yield may be attributed to the greater solubility of the starting material. The final step of the synthesis involved cyclization and removal of the methoxy protecting group. Fortunately, treatment of compound (**111**) with sodium iodide and methyl iodide converted the phenylsulfide moiety to an iodide, cyclized it to the pyridine nitrogen, and removed the protecting group to provide the lactam (**26**) in 80 % yield. Compound (**26**) is the demethoxy analog of harmalanine (**27**); so it is conceivable that one could synthesize harmalanine (**27**) by starting with an analog of imine (**70**) which contains a methoxy group situated at the appropriate position. It is also conceivable that compound (**26**) could be formylated to form nauclefidine (**28**), giving support to the assertion that our pathway is general for a wide variety of natural products.

Scheme XIX



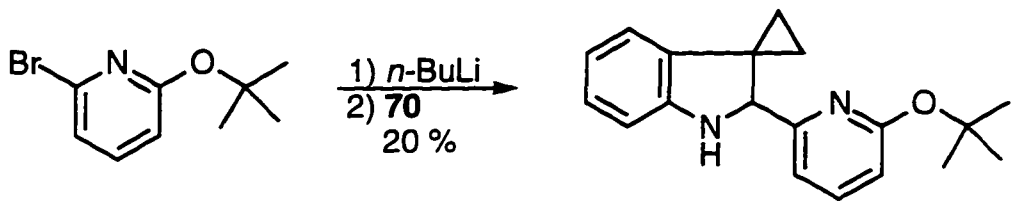
(**70**) (**108**) (**109**)

(**110**)

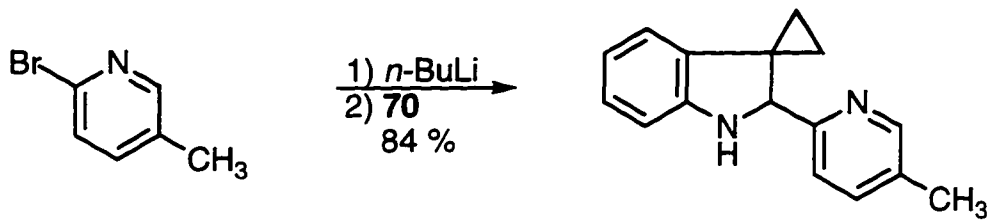
(**111**) (**26**)

To further support the generality of our synthetic pathway, we reacted the imine (**70**) with a couple of different pyridines. In the first case (Scheme XX), the lithium anion of 2-bromo-6-*tert*-butoxypyridine (**112**) was generated and quenched with the imine (**70**) to provide compound (**113**). Unfortunately, this reaction was generally low-yielding and irreproducible, quite unlike its methoxy counterpart. The second reaction that we performed was to alkylate the imine (**70**) with the anion of 2-bromo-5-methylpyridine (**114**) to give compound (**115**) in 84 % crude yield. This reaction had its drawback in that compound (**115**) was very sensitive to chromatography (both silica gel and alumina) and purification was not possible. However, the crude compound was generally pure enough to be used in further reactions without much trouble.

Scheme XX

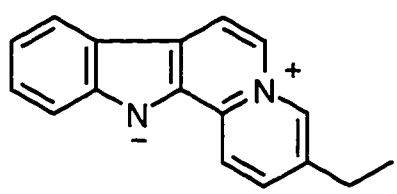


(**112**) (**113**)

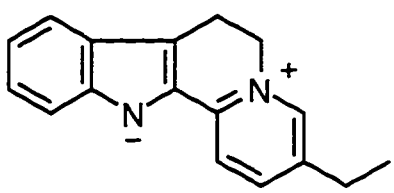


(**114**) (**115**)

The formation of compounds such as (**115**) shows that this process could be used for the synthesis of flavopereirine (**20**) or its 6,7-dihydro analog (**22**), both of which have interesting biological activities.[6] Substitution of the methyl substituent at the 5-position of the pyridine ring with an ethyl group and subjecting it to the same sequence of reaction in Scheme XIX could conceivably lead to both compounds (**20**) and (**22**). The only reason that the 5-methyl analog was chosen in our model study was because the corresponding 2-bromo-5-methylpyridine was commercially available at the time and the 2-bromo-5-ethylpyridine was not.



(**20**)



(**22**)

Conclusions

We have developed a route that completes four of the five rings of eburnamonine (**1**) and contains functional handles to complete the synthesis. This

same route has also been used to complete a synthesis of the natural product indolo[2,3-*a*]pyridocoline (**19**), and this pathway has been shown to be applicable to several other analogs of the indolo[2,3-*a*]quinolizine family. Along the way, we have discovered some interesting methodology involving the attack of nucleophiles at the 2-position of an indole ring system. This is a very unique method of constructing bonds in this type of system. Finally, we have also improved known methods of lithiating 2-bromopyridines at the 3-position.

Experimental

Unless otherwise noted, materials were obtained from commercial suppliers and used without additional purification. Diethyl ether and tetrahydrofuran (THF) were distilled from sodium benzophenone ketyl. Benzene was distilled from lithium aluminum hydride. Toluene and methanol were distilled from sodium. Dichloromethane (CH_2Cl_2), and acetonitrile were distilled from calcium hydride. All reactions were conducted under an argon atmosphere and all extracts were dried over anhydrous sodium sulfate or anhydrous magnesium sulfate. Apparatus for experiments requiring anhydrous conditions were flame-dried under a stream of argon or dried in a 150 °C oven for 12 hours and cooled under a stream of argon. Alumina chromatography was conducted using activated neutral aluminum oxide, Brockmann I, standard grade (150 mesh), which was purchased from Aldrich Chemical Company. Silica gel chromatography (sgc) was performed on EM Science Kieselgel 60 (mesh 230-400). Thin layer chromatography (tlc) was performed using EM Science Kieselgel F_{254} prepared plates with a thickness of 0.25 mm. The solvent systems were suitable mixtures of hexanes (H) and ethyl acetate (EA) unless otherwise noted. Infrared spectra were obtained on a Perkin-Elmer 1320 spectrophotometer and are reported in cm^{-1}. Proton nuclear magnetic resonance spectra (300 MHz) were obtained using a Nicolet Magnetics Corporation NMC-1280 spectrometer. All chemical shifts are reported in δ relative to tetramethylsilane as an internal standard. Splitting patterns are designated as s (singlet), d (doublet), t (triplet), q (quartet), dd (doublet of doublets), dt (doublet of

triplets), and m (multiplet); the addition of br indicates a broadened pattern. Carbon-13 NMR spectra (75.46 MHz) were obtained on a Nicole NMC-1280 spectrometer and are reported in δ relative to $CDCl_3$ (77.00 ppm) as an internal standard. High resolution mass spectra (HRMS) were obtained on a Kratos model MS-50 spectrometer. Low resolution mass spectra (MS) were obtained on a Finnigan 4023 mass spectrometer. The purity of all title compounds was determined to be > 90 % by ^1H NMR spectral determination.

Spiro[cyclopropane-1,3'-[3*H*]indole] (70). Following the procedure of Rapoport,[31] anhydrous potassium carbonate (8.91 g, 64.4 mmol) was added to a solution of 3-(2-bromoethyl)indole (**69**) (3.61 g, 16.1 mmol) in 125 mL of acetonitrile. The solution was refluxed for 8 hours and filtered through a glass frit. Concentration afforded 2.22 g (96 %) of a yellow oil, which was generally pure enough to be used without further purification. However, vacuum pump distillation [75 °C (0.3 mm)] can be used to obtain the compound as a low-melting white solid. ^1H NMR ($CDCl_3$) δ 1.76 - 1.81 (m, 2H), 1.99 - 2.04 (m, 2H), 7.04 - 7.36 (m, 3H), 7.75 (dd, J_1 = 7.8 Hz, J_2 = 0.7 Hz, 1H). IR (film) 3054, 3007, 1528, 1448, 1234, 964, 767, 746 cm^{-1}.

Spiro[cyclopropane-1,3'-(2'-pyridin-2-yl)indoline] (75). To a solution of 2-bromopyridine (0.864 g, 5.47 mmol) in 25 mL of THF at -78 °C was added *n*-BuLi (5.74 mmol, 2.50 ml of a 2.3 M solution in hexanes) dropwise. The solution was stirred for 1 hour at -78 °C. The imine (**70**) was added via cannula in 5 mL of THF, and the solution stirred for 1 hour. The mixture was quenched with saturated $NaHCO_3$ and extracted with ether. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated. The crude product was purified by flash column chromatography on neutral alumina using deoxygenated solvents (20:1 H:EA to 100 % EA) to afford 0.846 g (69 %) of a yellow oil. ^1H NMR ($CDCl_3$) δ 0.48 - 0.53 (m, 1H), 0.66 - 0.71 (m, 1H), 1.07 - 1.13 (m, 2H), 4.97 (s, 1H),

6.61 (d, J = 5.7 Hz, 1H), 6.70 - 6.75 (m, 2H), 7.04 (dt, J_1 = 0.6 Hz, J_2 = 5.7 Hz, 1H), 7.16 - 7.19 (m, 1H), 7.53 (d, J = 6.0 Hz, 1H), 7.66 (dt, J_1 = 1.5 Hz, J_2 = 5.7 Hz, 1H), 8.50 (dd, J_1 = 3.6 Hz, J_2 = 0.6 Hz, 1H). IR (film) 3364, 3053, 1610, 1591, 1471, 1230, 909, 741 cm^{-1}. MS (CI) m/z 223, 203, 136. HRMS m/z calculated for $C_{15}H_{14}N_2$: 222.1157, measured 222.1157. ^{13}C NMR ($CDCl_3$) δ 13.7, 15.8, 29.9, 68.7, 108.3, 118.2, 118.7, 121.0, 122.0, 126.6, 133.2, 136.4, 148.2, 150.3, 161.4. TLC (7:1 H:EA, alumina plates) R_f = 0.37.

Spiro[cyclopropane-1,3'-(2'-pyridin-2-yl)-[3*H*]indole] (85). To a solution of compound (**75**) (0.846 g, 3.81 mmol) in 50 mL of CH_2Cl_2 was added 25 mL of Chlorox bleach. The solution was stirred overnight at room temperature and monitored by TLC. Occasionally, more bleach had to added to ensure complete consumption of starting material. The two layers were separated, and the organic layer was concentrated to give 0.838 g (100 %) of a yellow wax, which was used without further purification. ^1H NMR ($CDCl_3$) δ 1.93 (AB quartet, J_1 = 2.9 Hz, J_2 = 7.7 Hz, 2H), 2.92 (AB quartet, J_1 = 2.9 Hz, J_2 = 7.7 Hz, 2H), 7.05 - 7.08 (m, 1H), 7.25 - 7.32 (m, 2H), 7.38 (dt, J_1 = 1.2 Hz, J_2 = 7.6 Hz, 1H), 7.75 - 7.83 (m, 2H), 8.48 (dt, J_1 = 1.0 Hz, J_2 = 8.0 Hz, 1H), 8.57 (m, 1H). IR (film) 3053, 3006, 1632, 1587, 1441, 742 cm^{-1}. MS (CI) m/z 221, 117. HRMS m/z calculated for $C_{15}H_{11}N_2$ (M^+ - 1): 219.0922, measured 219.0921. ^{13}C NMR ($CDCl_3$) δ 21.8, 36.7, 117.1, 121.1, 122.4, 124.1, 125.3, 126.3, 136.2, 143.2, 148.7, 153.0, 153.8, 175.7. TLC - not stable.

3-(2-Phenylthioethyl)-2-(2-pyridyl)indole (96). To a solution of thiophenol (0.64 mL, 6.18 mmol) in 10 mL of THF was added BuLi (3.71 mmol, 1.5 mL of a 2.4 M solution in hexanes) dropwise at 0 °C, and the solution was stirred for 20 minutes. The thiophenoxide anion solution was added via cannula to the heterogeneous solution of compound (**85**) (0.544 g, 2.47 mmol) in 4 mL of THF. The reaction was followed by TLC and quenched with saturated $NaHCO_3$. The aqueous layer was extracted twice with CH_2Cl_2 and dried over Na_2SO_4. The crude

product was purified by flash column chromatography on neutral alumina using deoxygenated solvents (20:1 H:EA to 1:2 H:EA) to afford 0.196 g (24 %) of a yellow oil. ^{1}H NMR ($CDCl_3$) δ 3.21 - 3.26 (m, 2H), 3.37 - 3.43 (m, 2H), 7.10 - 7.64 (m, 12H), 8.61 (dd, J_1 = 4.8 Hz, J_2 = 0.6 Hz, 1H), 9.61 (bs, 1H). IR (film) 3440, 3055, 1589, 1436, 738 cm^{-1}. MS (CI) m/z 331. HRMS m/z calculated for $C_{21}H_{18}N_2S$: 330.1191, measured 330.1190. ^{13}C NMR ($CDCl_3$) δ 25.6, 34.1, 111.2, 113.2, 118.9, 119.5, 120.6, 121.5, 123.3, 126.4, 128.9, 129.2, 130.3, 132.3, 135.4, 135.9, 136.7, 149.2, 150.4. TLC (20:1 H:EA, alumina plates) R_f = 0.28.

6,7-Dihydroindolo[2,3-*a*]quinolizin-5(12*H*)-ium perchlorate (106). The following is a modification of a procedure by Corey.[42] Into a sealed tube was placed compound (**96**) (0.196 g, 0.593 mmol), NaI (0.445 g, 2.97 mmol) in 5 mL of *N,N* - dimethylformamide. Methyl iodide (2 mL) was added, and the solution heated at 80 °C for eight hours. The solvent was removed via vacuum distillation, and the remaining solid was dissolved in CH_2Cl_2. The organic solution was extracted with 3M HCl (5 X 10 mL). The aqueous layer was concentrated to 15 - 20 mL and then added dropwise to a solution of sodium perchlorate hydrate (4.0 g in 10 mL of H_2O). The solution was filtered and washed with cold water to afford 0.064 g (34 %) of an orange-yellow solid: mp 258 °C (dec.). Literature value[21]: mp 255 -257 °C. Mass spectra of the perchlorate salt could not be obtained. Therefore, the zwitterionic structure was isolated by treating the salt with aqueous KOH and extracting with chloroform. ^{1}H NMR (D_6-DMSO) δ 3.56 (t, J = 7.5 Hz, 2H), 5.15 (t, J = 7.4 Hz, 2H), 7.18 - 7.90 (m, 5H), 8.31 (dd, J_1 = 6.4 Hz, J_2 = 0.6 Hz, 1H), 8.59 (dt, J_1 = 8.2 Hz, J_2 = 1.3 Hz, 1H), 8.99 (dd, J_1 = 6.2 Hz, J_2 = 0.6 Hz, 1H). IR (film) 3327, 1634, 1557, 1100, 747, 623 cm^{-1}. MS (CI) m/z of the zwitterion 221, 195. HRMS m/z calculated for $C_{15}H_{11}N_2$ (M^+- 1): 219.0922, measured 219.0922. UV-Vis (MeOH) λ_{max} 252, 314, 386. UV-Vis (MeOH / KOH) λ_{max} 254, 316, 402.

Indolo[2,3-*a*]quinolizin-5(12*H*)-ium perchlorate (107). Following the procedure of Fürstner,[21] to a suspension of compound (**106**) (0.064 g, 0.200 mmol) in 5 mL of acetic acid was added DDQ (0.135 g, 0.600 mmol), and the solution refluxed overnight. Another portion of DDQ (0.135 g, 0.600 mmol) was added, and the solution was refluxed for another five hours. The solution was diluted with ethanol and concentrated. The remaining solid was diluted with 2N NaOH and extracted with chloroform. The organic layer was acidified with 6N HCl and extracted several times (4 X 10 mL). The aqueous layer was concentrated to approximately 5 mL and then added dropwise to a solution of sodium perchlorate hydrate (4.0 g in 10 mL of H_2O). The solution was filtered and washed with cold water to afford 0.049 g (77 %) of green-yellow crystals: mp 283 °C (dec). Literature value[21]: mp 282 - 285 °C (dec). Mass spectra of the perchlorate salt could not be obtained. Therefore, the zwitterionic structure was isolated by treating the salt with aqueous KOH and extracting with chloroform. ^{1}H NMR (D_6-DMSO) δ 7.44 (t, J = 7.3 Hz, 1H), 7.70 (dt, J_1 = 7.1 Hz, J_2 = 0.7 Hz, 1H), 7.83 (d, J = 8.3 Hz, 1H), 7.98 (dt, J_1 = 6.2 Hz, J_2 = 0.8 Hz, 1H) 8.38 - 8.43 (m, 2H), 8.79 (d, J = 6.9 Hz, 1H), 8.98 - 9.06 (m, 2H), 9.38 (d, J = 6.8 Hz, 1H). IR (film) 3587, 1647, 1630, 1472, 1375, 1111, 618 cm^{-1}. MS (CI) m/z of the zwitterion 218. HRMS m/z calculated for $C_{15}H_{10}N_2$: 218.0844, measured 218.0844. UV-Vis (MeOH) λ_{max} 218, 238, 246, 294, 326, 340, 358, 386. ^{13}C NMR (D_6-DMSO) δ 113.0, 116.9, 120.7, 121.8, 122.0, 122.3, 123.1, 124.3, 127.6, 129.7, 130.8, 132.5, 136.0, 137.2, 141.5.

Spiro[cyclopropane-1,3'-(2'-(6-methoxy)pyridin-2-yl)indoline] (109). To a solution of 2-bromo-6-methoxypyridine (**108**)[43] (1.44 g, 6.09 mmol) in 25 mL of THF at -78 °C was added *n*-BuLi (6.39 mmol, 2.80 ml of a 2.3 M solution in hexanes) dropwise. The solution was stirred for 1 hour at -78 °C. The imine (**70**) was added via cannula in 5 mL of THF, and the solution stirred for 1 hour. The mixture was quenched with saturated $NaHCO_3$ and extracted with ether. The combined organic layers were washed with brine, dried over Na_2SO_4, and

concentrated. The crude product was purified by flash column chromatography on neutral alumina using deoxygenated solvents (30:1 H:EA to 100 % EA) to afford 1.13 g (73 %) of a yellow oil. ^{1}H NMR ($CDCl_3$) δ 0.61 - 0.71 (m, 2H), 1.06 - 1.19 (m, 2H), 3.87 (s, 3H), 4.83 (s, 1H), 6.58 - 6.62 (m, 2H), 6.70 - 6.75 (m, 2H), 7.01 - 7.08 (m, 2H), 7.54 (dd, J_1 = 7.0 Hz, J_2 = 8.0 Hz, 1H). IR (film) 3370, 2996, 1610, 1488, 1029, 742 cm^{-1}. MS (CI) m/z 253, 251, 224, 144. HRMS m/z calculated for $C_{16}H_{16}N_2O$: 252.1263, measured 252.1268. ^{13}C NMR ($CDCl_3$) δ 13.6, 15.7, 29.9, 53.0, 68.3, 108.6, 108.7, 113.1, 118.3, 118.9, 126.7, 133.8, 139.0, 150.6, 159.1, 163.1. TLC (10:1 H:EA, alumina plates) R_f = 0.86.

Spiro[cyclopropane-1,3'-(2'-(6-methoxy)pyrid-2-yl)-[3*H*]indole] (110). To a solution of compound (**109**) (0.361 g, 1.43 mmol) in 10 mL of CH_2Cl_2 was added 7 mL of Chlorox bleach. The solution was stirred overnight at room temperature and monitored by TLC. Occasionally, more bleach had to added to ensure complete consumption of starting material. The two layers were separated, and the organic layer was concentrated to give 0.324 g (91 %) of a yellow wax, which was used without further purification. ^{1}H NMR ($CDCl_3$) δ 1.92 (AB quartet, J_1 = 3.3 Hz, J_2 = 7.9 Hz, 2H), 2.94 (AB quartet, J_1 = 3.4 Hz, J_2 = 7.9 Hz, 2H), 3.96 (s, 3H), 6.80 (dd, J_1 = 0.8 Hz, J_2 = 8.3 Hz, 1H), 7.05 (dd, J_1 = 7.4 Hz, J_2 = 0.6 Hz, 1H), 7.26 (dt, J_1 = 7.5 Hz, J_2 = 1.0 Hz, 1H), 7.38 (dt, J_1 = 1.2 Hz, J_2 = 7.6 Hz, 1H), 7.68 (t, J = 7.9 Hz, 1H), 7.81 (d, J = 7.8 Hz, 1H), 8.10 (dd, J_1 = 7.5 Hz, J_2 = 0.7 Hz, 1H). IR (film) 3008, 1589, 1573, 1465, 1298, 1265, 744 cm^{-1}. MS (CI) m/z 251, 205. HRMS m/z calculated for $C_{16}H_{14}N_2O$: 250.1106, measured 250.1105. ^{13}C NMR ($CDCl_3$) δ 21.1, 36.3, 53.0, 111.7, 115.5, 116.9, 121.0, 125.1, 126.3, 138.7, 142.9, 150.0, 153.8, 163.1, 175.4. TLC - not stable.

2-[2-(5-Methoxy)pyridyl]-3-(2-phenylthioethyl)indole (111). To a solution of thiophenol (0.34 mL, 3.34 mmol) in 6 mL of THF was added BuLi (1.75 mmol, 0.72 mL of a 2.4 M solution in hexanes) dropwise at -20 °C, and the solution

was stirred for 45 minutes. The thiophenoxide anion solution was added via cannula to the heterogeneous solution of compound (**110**) (0.418 g, 1.67 mmol) in 4 mL of THF at -78 °C. The reaction was followed by TLC and quenched with saturated $NaHCO_3$. The aqueous layer was extracted twice with ether, washed with brine and dried over Na_2SO_4. The crude product was purified by flash column chromatography on neutral alumina using deoxygenated solvents (30:1 H:EA to 7:1 H:EA) to afford 0.373 g (62 %) of a yellow oil which crystallized over time: mp 83 - 84 °C. ^1H NMR ($CDCl_3$) δ 3.22 - 3.27 (m, 2H), 3.39 - 3.45 (m, 2H), 4.05 (s, 3H), 6.66 (d, J = 8.2 Hz, 1H), 7.06 (d, J = 7.5 Hz, 1H), 7.12 - 7.60 (m, 10H), 9.18 (bs, 1H). IR (film) 3420, 1589, 1574,1469, 1025, 737 cm^{-1}. MS (CI) m/z 361. HRMS m/z calculated for $C_{21}H_{18}N_2S$: 360.1296, measured 360.1304. ^{13}C NMR ($CDCl_3$) δ 25.5, 34.0, 53.3, 108.8, 111.0, 113.2, 113.4, 118.9, 119.6, 123.3, 126.3, 128.9, 129.3, 130.1, 132.1, 135.0, 136.1, 139.2, 147.9, 163.4. TLC (10:1 H:EA, alumina plates) R_f = 0.51.

7,12-Dihydroindolo[2,3-*a*]quinolizin-4(6*H*)-one (26). The following is a modification of a procedure by Corey.[42] Into a sealed tube was placed compound (**111**) (0.357 g, 0.990 mmol), NaI (1.50 g, 9.90 mmol) in 5 mL of *N,N*-dimethylformamide. Methyl iodide (2 mL) was added, and the solution heated at 80 °C for 24 hours. The solvent was removed via vacuum distillation, and the remaining solid was dissolved in CH_2Cl_2 and washed with water. The solution was dried over Na_2SO_4 and concentrated. The crude product was purified by chromatographing over silica gel ($CHCl_3$ to 20:1 $CHCl_3$:MeOH) to give an off-white solid 0.116 g (80 %). ^1H NMR ($CDCl_3$) δ 3.11 (t, J = 7.1 Hz, 2H), 4.46 (t, J = 6.9 Hz, 2H), 6.33 (dd, J_1 = 7.1 Hz, J_2 = 1.0 Hz, 1H), 6.53 (dd, J_1 = 9.1 Hz, J_2 = 1.1 Hz, 1H) 7.15 - 7.42 (m, 4H), 7.59 (d, J = 7.7 Hz, 1H) 8.37 (bs, 1H). IR (film) 3244, 2918, 1651, 1568, 799, 741 cm^{-1}. MS (CI) m/z 237. HRMS m/z calculated for $C_{15}H_{12}N_2O$: 236.0950, measured 236.0944. ^{13}C NMR ($CDCl_3$) δ 19.6, 40.4, 99.7, 111.6, 114.8,

118.5, 119.6, 120.7, 124.7, 125.9, 127.5, 137.8, 138.2, 138.5, 162.9. TLC (20:1 $CHCl_3$:MeOH) R_f = 0.62.

2-Bromo-6-(1,1-dimethylethoxy)pyridine (112). To a solution of 2,6-dibromopyridine (4.01 g, 16.9 mmol) and 25 mL of *tert*-butanol was added potassium *tert*-butoxide (3.22 g, 28.7 mmol). The solution was heated at reflux for a period of 12 hours, during which the solution became totally homogeneous. The solution was quenched with saturated with $NaHCO_3$ and extracted with ether. The organic layer was washed with brine and dried over $MgSO_4$. After concentrating, the solution was distilled under vacuum to give 2.53 g (65 %) of a white solid that melts at room temperature. ^1H NMR ($CDCl_3$) δ 1.58 (s, 9H), 6.57 (dd, J_1 = 8.3 Hz, J_2 = 0.5 Hz, 1H), 6.97 (d, J = 7.6 Hz, 1H), 7.34 (t, J = 8.2 Hz 1H). IR (film) 2930, 1589, 1548, 1434, 938, 785 cm^{-1}. MS(CI) m/z 231. ^{13}C NMR ($CDCl_3$) δ 28.5, 80.9, 111.5, 119.5, 137.7, 140.1, 163.0. TLC (20:1 H:EA) R_f = 0.69.

Spiro[cyclopropane-1,3'-(2'-[6-(1,1-dimethylethoxy)]pyridin-2-yl)-[3*H*]indole] (113). To a solution of 2-bromo-6-*tert*-butoxypyridine (**112**) (0.329 g, 2.30 mmol) in 9 mL of THF at -78 °C was added *n*-BuLi (2.30 mmol, 0.95 ml of a 2.4 M solution in hexanes) dropwise. The solution was stirred for 1 hour at -78 °C. The imine (**70**) was added via cannula in 2 mL of THF, and the solution stirred for 1 hour. The mixture was quenched with saturated $NaHCO_3$ and extracted with ether. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated. The crude product was purified by flash column chromatography on neutral alumina using deoxygenated solvents (50:1 H:EA to 10:1 H:EA) to afford 0.127 g (20 %) of a yellow oil. ^1H NMR ($CDCl_3$) δ 0.68 - 0.81 (m, 2H), 1.08 - 1.17 (m, 2H), 1.53 (s, 9H), 4.74 (s, 1H), 6.55 - 6.77 (m, 4H), 6.95 (d, J = 7.3 Hz, 1H), 7.06 (dt, J_1 = 7.6 Hz, J_2 = 1.1 Hz, 1H) 7.50 (t, J = 7.8 Hz, 1H). IR (film) 3374, 2975, 1570, 1488, 1437, 739 cm^{-1}. MS (CI) m/z 295, 239, 210. ^{13}C NMR ($CDCl_3$) δ 13.1, 17.3, 28.5, 30.2, 69.0, 79.3, 108.6, 111.6, 112.8, 118.3, 118.8,

126.6, 133.9, 138.6, 150.9, 158.8, 163.2. TLC (30:1 H:EA, alumina plates) R_f = 0.57.

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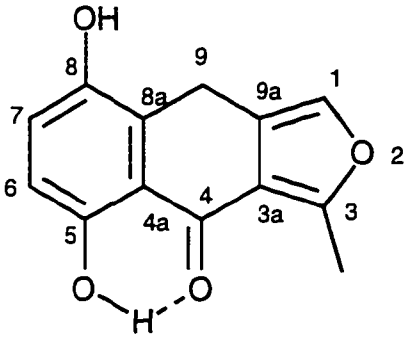
CHAPTER 2. A SYNTHETIC APPROACH TO MS-444

A paper to be submitted to the Journal of Organic Chemistry

George A. Kraus and John H. Malpert

Introduction

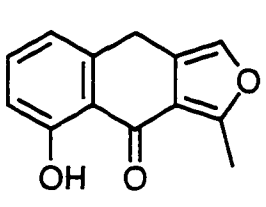
In September of 1995 two researchers, Aotani and Saitoh, at the Tokyo Research Laboratories reported that they had characterized a novel natural product that possessed a rather unusual ring system.[1] This compound, which had been given the name MS-444 (**1**), contained a unique 4(9*H*)-naphtho[2,3-*c*]furanone ring structure. This type of structure had only been reported in the literature twice before as an intermediate in the synthesis of aromatic *ortho*-diketones.[2] This was the first instance in which this particular structure had been isolated from natural sources.



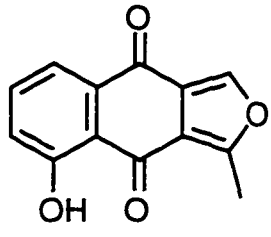
(**1**)

Shortly thereafter, during the revision of Saitoh's manuscript, Koyama and co-workers isolated several new compounds from the plant *Aloe ferox*.[3] MS-444 (**1**) was not one of the natural products discovered from this plant; however, three closely related analogs were. Among those derivatives was 5-hydroxy-3-methyl-

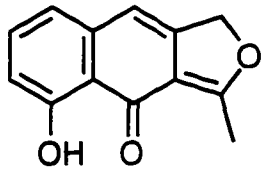
naphtho[2,3-*c*]furan-4(9*H*)-one (**2**), which is almost identical to MS-444 except for the lack of a phenolic hydroxyl group at the 8-position. The second and third analogs which were isolated did not contain the 4(9*H*)-naphtho[2,3-*c*]furanone ring structure *per se*, but they were very similar in structure. One analog (**3**) contained an extra carbonyl at the 9-position as well as lacking the phenolic hydroxyl group. The other derivative (**4**) contained a dihydrofuran moiety where the double bond had migrated to the 9-9a position. As of this date, compounds (**1**) and (**2**) are the only compounds isolated from nature which contain the 4(9*H*)-naphtho[2,3-*c*]furanone ring system.



(**2**)



(**3**)



(**4**)

Originally, MS-444 (**1**) had been isolated in the same Tokyo Research Laboratories by five different researchers.[4] These researchers were screening the culture broth of a bacterial strain KY7123, which was taken from a soil sample collected in Okinawa, Japan. They discovered the compound, and they were the ones responsible for designating it as MS-444 (**1**). The bacterial strain was eventually identified from its cultural and morphological characteristics as *Micromonospora* sp. In a typical procedure, 15 liters of bacterial culture gave approximately 100 mg of pure MS-444 (**1**), after extraction, purification by three different silica gel chromatographies and then crystallization. These researchers

also discovered that MS-444 (**1**) had biological activity as it inhibited myosin light chain kinase.

Myosin light chain kinase is a regulatory enzyme in smooth muscle contraction.[5,6] Contraction stimuli, such as hormones and neurotransmitters, increase the concentration of Ca^{2+} in the cytoplasm and activate calmodulin. Calmodulin is a protein which binds Ca^{2+} in smooth muscle cells. When Ca^{2+} is bound, this protein activates myosin light chain kinase, which in turn catalyzes transfer of γ-phosphate of ATP to Ser-19 of 20-kDa myosin light chain. The phosphorylated myosin then interacts with actin to generate force for the contraction. This contractile property of smooth muscle cells is a major determinant of vascular tone and diameter of the bronchial tubes. Therefore, myosin light chain kinase inhibitors, such as MS-444 (**1**), could be potential vasodilators or bronchodilators.[4]

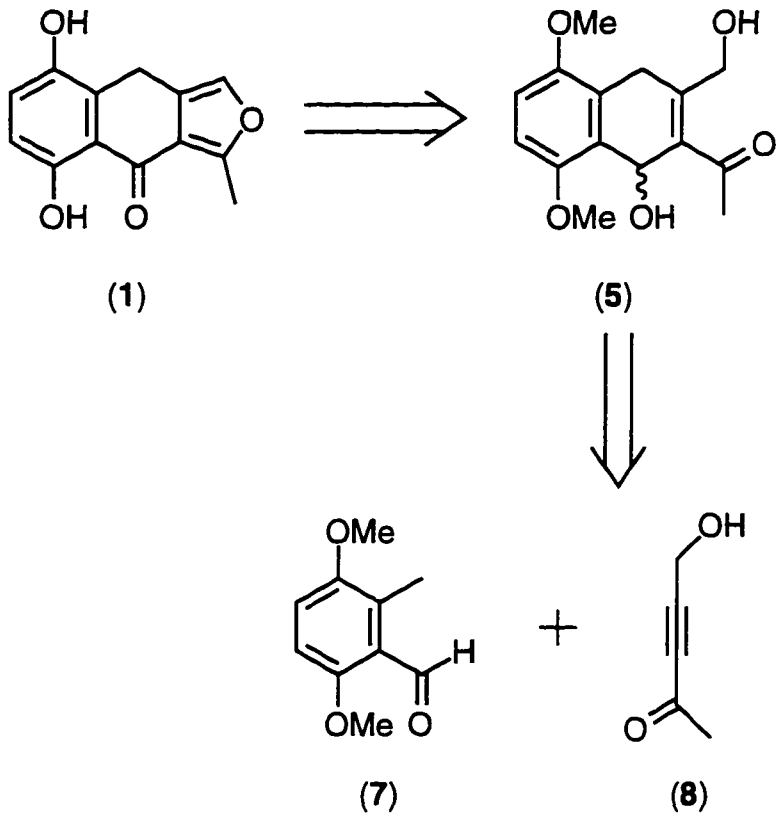
Nakanishi and co-workers showed that MS-444 (**1**) inhibited Ca^{2+} and calmodulin-dependent activity of smooth muscle myosin light chain kinase in a concentration-dependent manner. The concentration that was needed to inhibit the enzyme activity by 50 % (IC_{50}) was 10 μM. This is moderate when compared to other myosin light chain kinase inhibitors that have been reported. In addition, Nakanishi reports that MS-444 (**1**) has no antimicrobial activity at a concentration of 100 μg/mL.[4]

Results and Discussion

We became interested in MS-444 (**1**) because of its unique chemical bonding structure and inherent biological activity. At first we envisioned a photosynthetic pathway (Scheme I) to MS-444 (**1**). The final molecule would come from a precursor such as (**5**), which is the product of a tandem photoenolization/[4+2] cycloaddition reaction that has been well-studied in our group.[7] We had hoped that oxidation of a compound such as (**5**) would do two things. The first would be to oxidize the benzylic alcohol to the ketone needed in

MS-444 (**1**). The second would be to oxidize the primary allylic alcohol to the corresponding aldehyde, which should cyclize to hemiacetal and provide the desired furan upon elimination of water. The precursors to intermediate (**5**) would be molecules (**7**) and (**8**), which are easily synthesized from available materials.

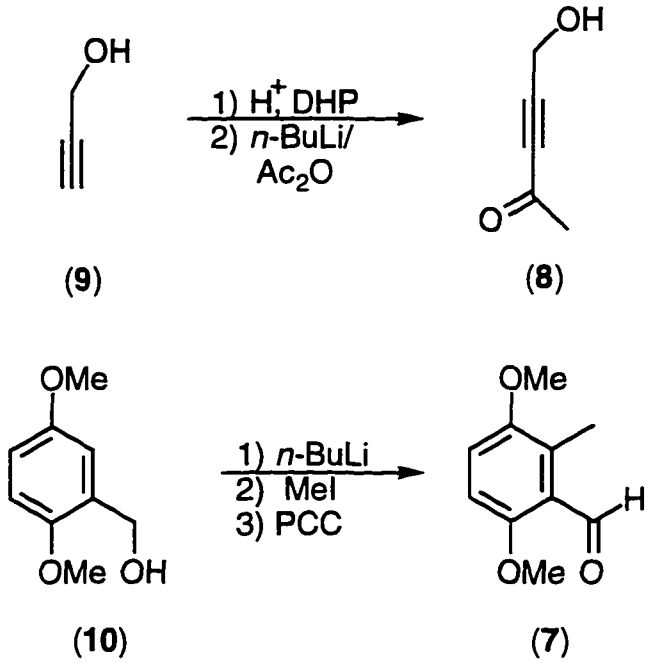
Scheme I



(**1**) (**5**) (**7**) (**8**)

We began the synthesis (Scheme II) by making compound (**8**) from propargyl alcohol (**9**) following the procedure of Duranti.[8] Propargyl alcohol (**9**) was first protected as its tetrahydropyranyl ether. This compound was then deprotonated with *n*-BuLi and quickly quenched with acetic anhydride to form compound (**8**) in a rather modest yield. On the other hand, compound (**7**) was prepared by treating 2,5-dimethoxybenzyl alcohol with *n*-BuLi and quenching with methyl iodide. Oxidation of the alcohol lead to the desired aldehyde (**7**).

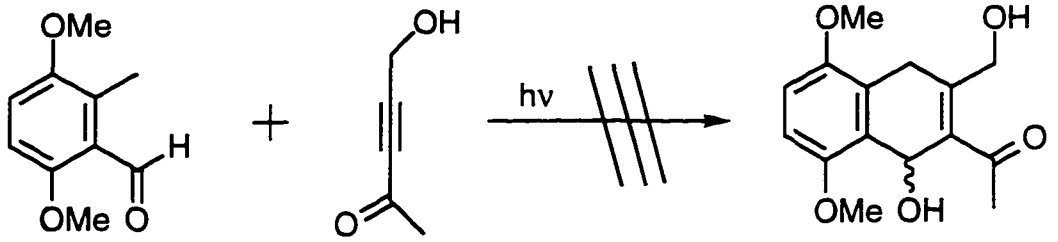
Scheme II



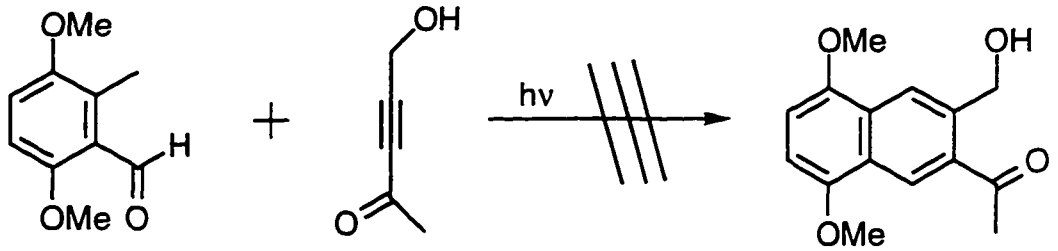
With compounds (**7**) and (**8**) in hand, we proceeded with the key photolysis reaction (Scheme III). We knew that a compound such as (**5**) would be prone to undergo elimination of the benzylic alcohol to provide a naphthalene compound such as (**11**) so extra care was taken to prevent such a sequence of events from occurring. However, after photolyzing compounds (**7**) and (**8**), we were surprised to find that neither the desired intermediate (**5**), nor the napthalene compound (**11**), was isolated. The compound which we did isolate was never identified, but it did not contain a furan ring or even a hydroxymethylene moiety. In addition, no naphthalene protons were visible in the ^{1}H NMR, leaving a puzzling mystery.

Because of the discouraging results from the tandem photoenolization/Diels-Alder strategy, we decided to focus on a different approach. The retrosynthetic analysis can be seen in Scheme IV. We envisioned that the furan ring of MS-444 (**1**) could be formed from a precursor such as compound (**12**) via a novel silver-mediated cyclization that we had developed in our group several years ago.[9] In the previous example, the cyclization had occurred intermolecularly by reacting an alkene with a β-keto ester. This new chemistry which we were proposing would be

Scheme III



(7) (8) (5)

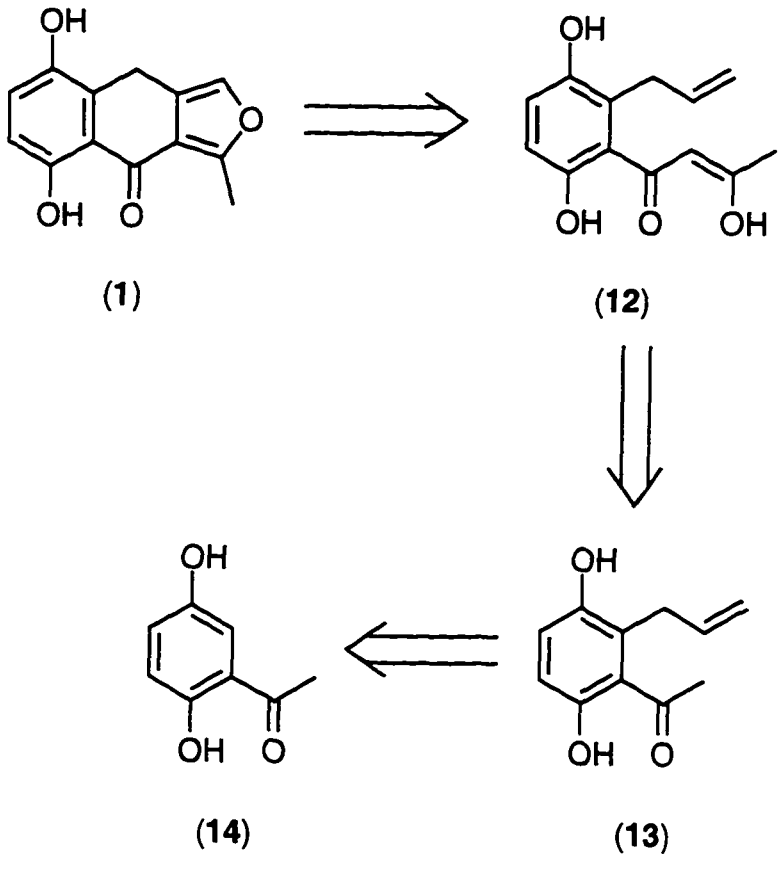


(7) (8) (11)

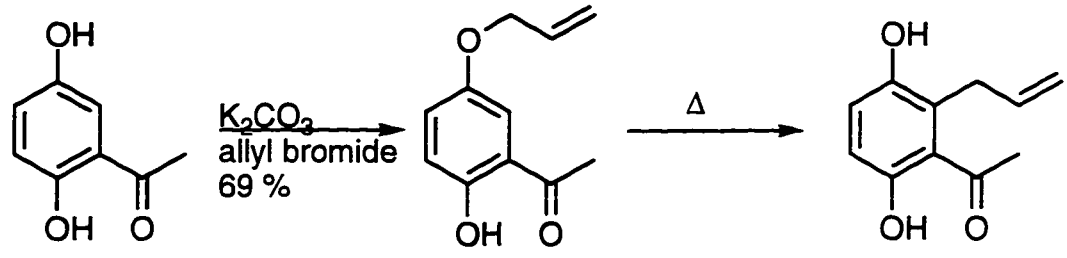
a natural extension involving an intramolecular version of the aforementioned reaction. Compound (**12**) would in turn be prepared from an intermediate such as compound (**13**) via a Baker-Ventkataraman reaction. Compound (**13**) would come from the readily available 2',5'-dihydroxyacetophenone (**14**) via a regioselective Claisen rearrangement. Once again, both of the aforementioned reactions, the Baker-Venkataraman[10] and the regioselective Claisen,[11, 12] had precedent within our group.

Starting with 2',5'-dihydroxyacetophenone (**14**), we were able to selectively allylate the phenol at the 5-position to get compound (**15**) in 69 % yield. This compound was then heated at 210 °C to selectively provide compound (**13**) in 60 % yield.

Scheme IV

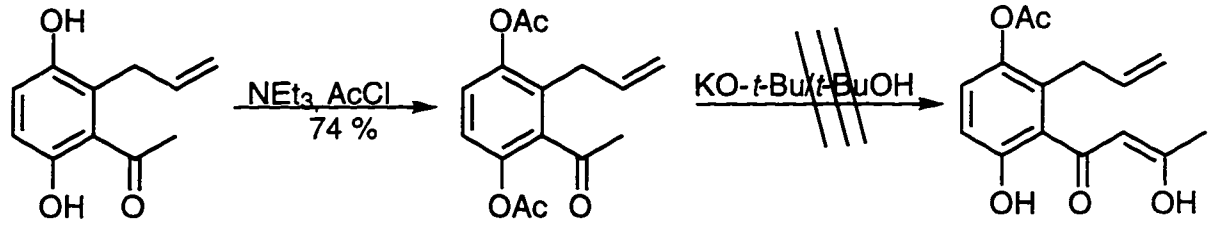


(1) (12) (13) (14)



(**14**) (**15**) (**13**)

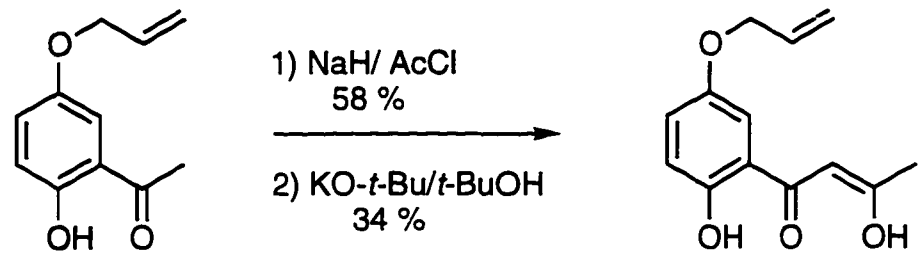
At this point, we needed to acetylate both of the phenols to position ourselves for the Baker-Ventkataramann reaction. Treating the diphenol (**13**) with an excess of triethylamine and quenching with acetyl chloride provided the diacetate (**16**) in 74 % yield. However, subjecting the compound (**16**) to the conditions of the Baker-Ventkataramann reaction did not provide any of the desired butanedione (**17**).



(**13**) (**16**) (**17**)

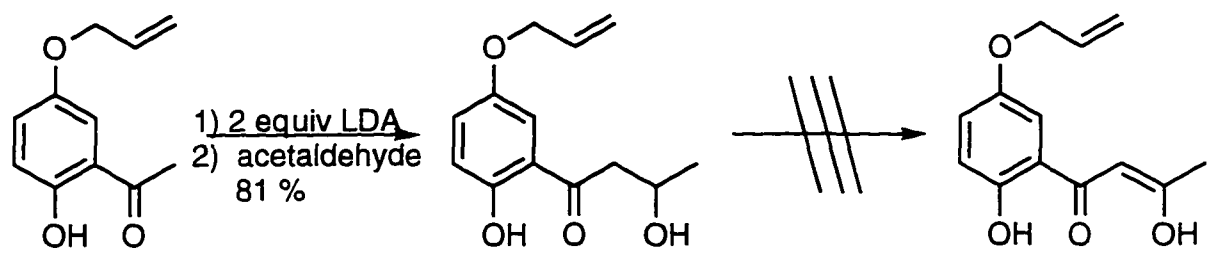
We felt that the acidic protons of the acetate at the 5-position may have been contributing to the failure of our reaction. Therefore, we decided to reverse the steps of our sequence, doing the Baker-Ventkataramann reaction before the Claisen rearrangement. By doing this, we were able to use the allyl group as a protecting group and then incorporate the protecting group into the molecule, thereby improving the efficiency of our synthetic sequence.

Therefore, we treated compound (**15**) with sodium hydride and acetyl chloride to obtain the acetate. Treating the acetate with potassium *tert*-butoxide/*tert*-butanol affirmed our assumptions as we were able to isolate the desired butanedione (**18**). Unfortunately, the yield was too low to be synthetically useful, and the decision was made to try other ways to make compound (**18**).



(**15**) (**18**)

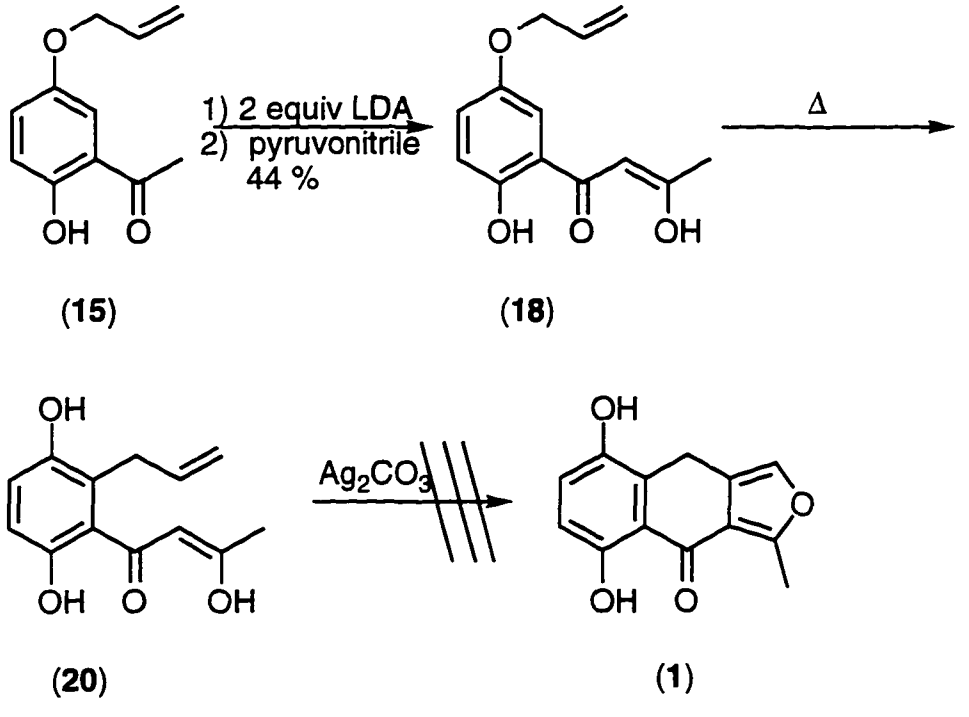
The first method that we tried involved generating the dianion of compound (**15**) and quenching with acetaldehyde to form the β-hydroxyketone (**19**) in an acceptable 81 % yield. However, a variety of oxidation conditions, including PCC and Jones oxidation conditions, failed to give the desired butanedione (**18**), and once again we were forced to find another route to compound (**18**).



(**15**) (**19**) (**18**)

We were able to find a somewhat acceptable solution using the acyl cyanide chemistry developed by Howard and co-workers.[13] Treating the acetophenone (**15**) (Scheme V) with two equivalents of lithium diisopropylamide and quenching with pyruvonitrile provided the desired 1,3-butanedione (**18**) in a modest 45 % yield. The allyl ether (**18**) was then subjected to the conditions of the Claisen rearrangement to provide compound (**20**) in 77 % yield. The reaction appeared to be completely selective in that none of the regioisomer with the allyl group at the 6-position was isolated.

Scheme V

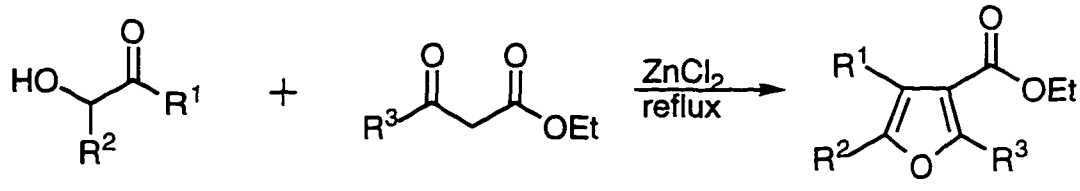


At this point, we were ready to try our silver-mediated cyclization reaction.[9] However, treating compound (**20**) (Scheme V) with freshly prepared silver carbonate did not generate the furan ring system as we had hoped. Only decomposition of the starting material occurred, and no useful products were

obtained from the reaction mixture. We had realized beforehand that oxidation of the hydroquinone moiety by the silver carbonate was a potential hazard to the success of our reaction, and unfortunately, we were unable to overcome this obstacle. Therefore, we decided to seek another alternative route.

At the same time that we were working on this project, we were also trying to make a highly functionalized furan in another one of our research endeavors. Upon exploring the furan chemistry developed by Hanson and co-workers,[14] we realized that we could synthesize a furan, such as compound (**22**) (Scheme VI), from the readily available ethyl acetoacetate (**24**) and 1,3-dihydroxyacetone (**25**). A furan with the appropriate leaving group as the X group could then be coupled with a metallated aryl ring (**23**) to form a compound such as (**21**). Cyclization of (**21**) could then be promoted by Friedel-Crafts conditions to provide MS-444 (**1**).

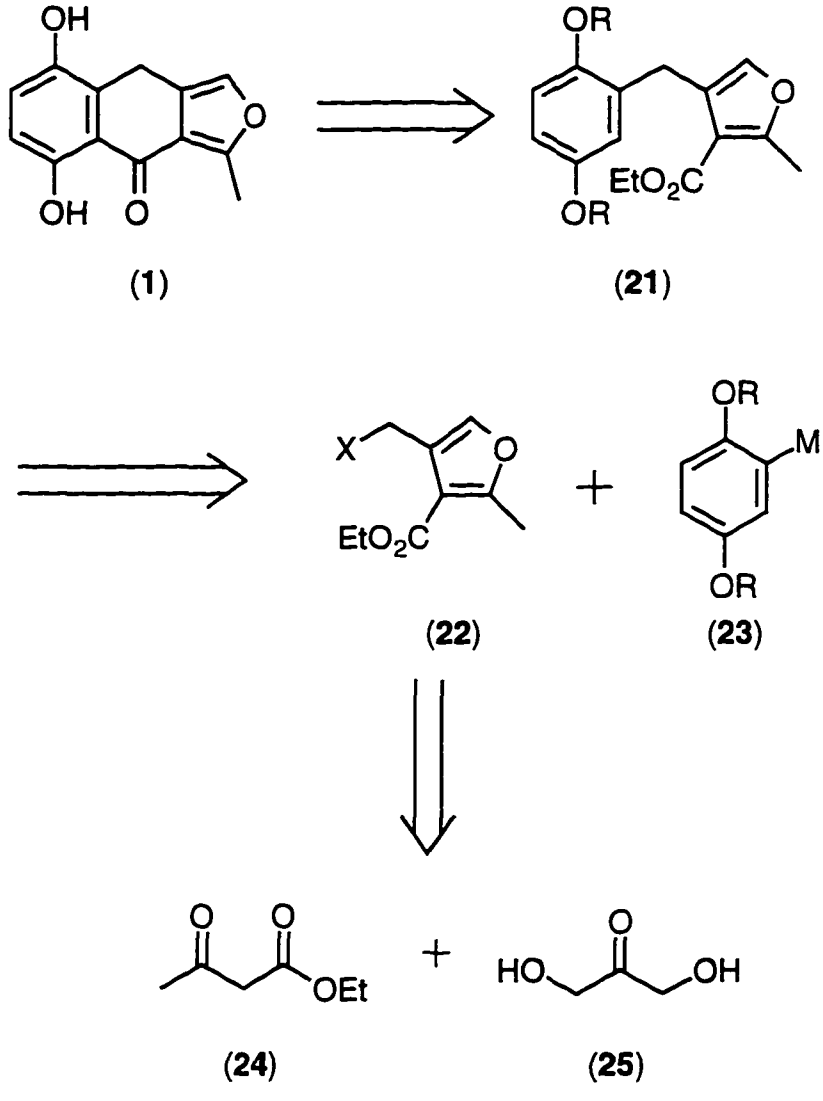
In 1965 Hanson and co-workers made a series of trisubstituted and tetrasubstituted furans (**28**) by reacting acyloins (**26**) with a variety of β-ketoesters (**27**) and zinc chloride in refluxing ethanol. However, in all cases R^1, R^2, and R^3 were either alkyl groups or aryl groups, and no attempt was made to functionalize any of the three substituents.



(**26**) (**27**) (**28**)

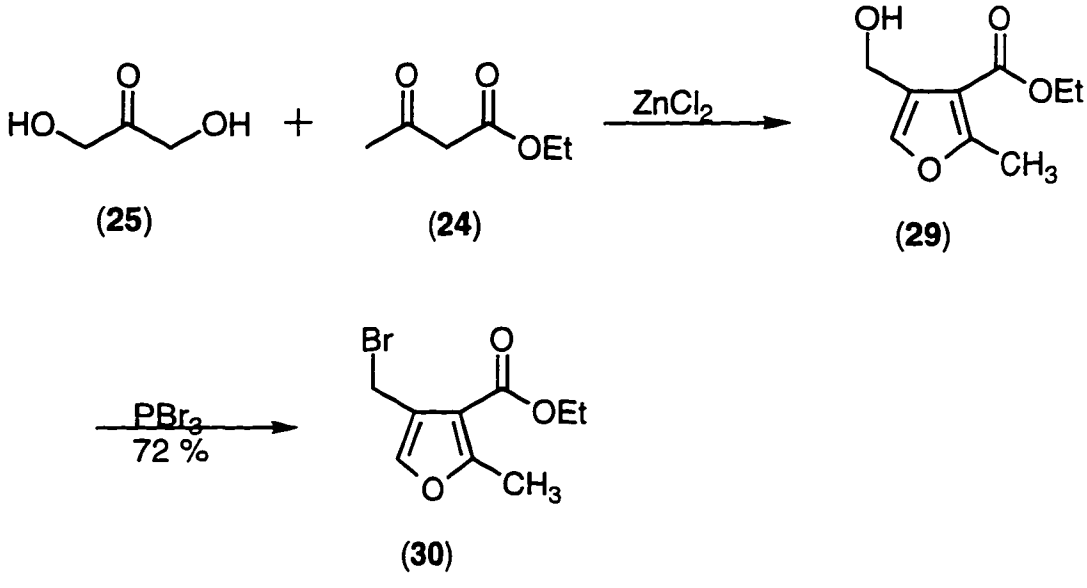
We tried to extend this chemistry by manipulating the R^1 group so that it would contain a functional group at the 4-position of the corresponding 3-furoate ester. We planned to use the symmetrical 1,3-dihydoxyacetone (**25**) as our acyloin to accomplish this feat. Using ethyl acetoacetate (**24**) as its counterpart would give us the furan (**29**) with the appropriate functionality at the 4-position. Upon trying

Scheme VI



this reaction (Scheme VII), we were pleased to discover that it gave the desired 4-hydroxymethylfuran (**29**) in almost quantitative yield. However, in contrast to the conditions specified by Hanson, this reaction could not be refluxed in ethanol as polymerization to the polyester tended to occur. The best yields were obtained when the reaction was allowed to run at room temperature over a period of two days, instead of refluxing for four hours as reported by Hanson.[14] The hydroxy group was then further manipulated by treating compound (**29**) with phosphorus tribromide to give the bromide (**30**) in 72 % yield. This compound was now set for the key coupling reaction with the metallated aryl ring.

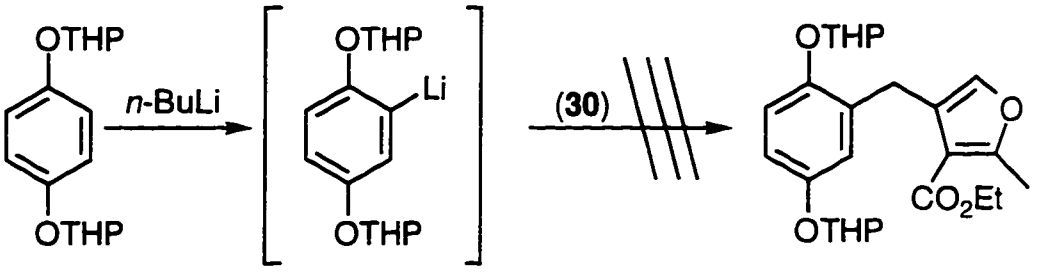
Scheme VII



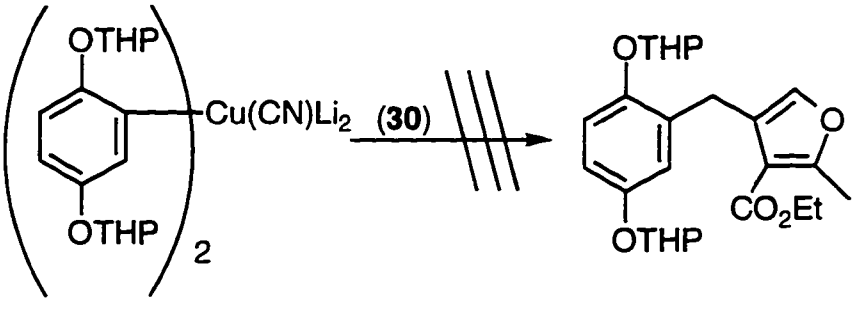
(**25**) (**24**) (**29**)

(**30**)

Our next endeavor was to design an appropriately protected hydroquinone. We originally chose the tetrahydropyranyl protecting group because of its simplicity to make and the mild conditions needed for its removal. Compound (**31**) was easily made from hydroquinone in near quantitative yield. Metallation with *n*-BuLi to provide the lithiated derivative (**32**) was a known procedure.[15] However, upon treating compound (**32**) with the bromide (**30**), no reaction occurred.



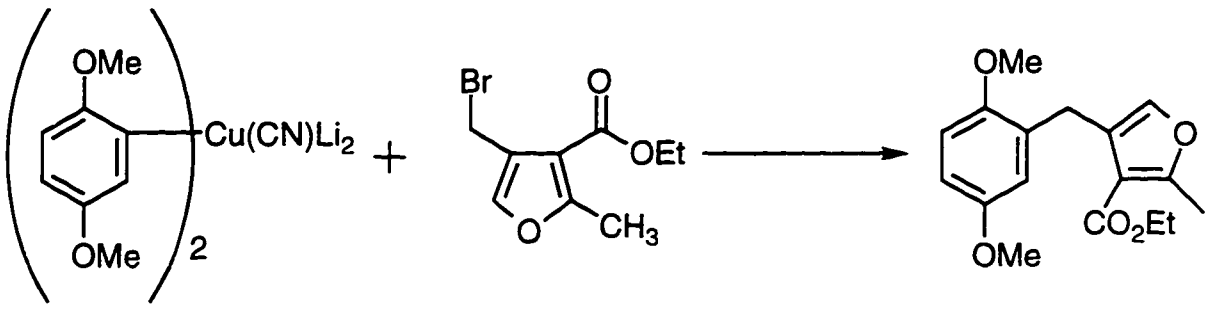
(31) (32) (33)



(34) (33)

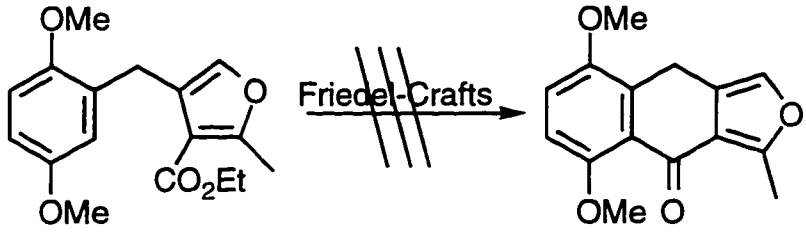
We then tried to couple the bromide (**30**) with the higher order cyanocuprate (**34**), according to the conditions of Lipshutz.[16] Once again we met with failure as none of the desired compound (**33**) was isolated.

We then decided that maybe the bulky tetrahydropyranyl protecting group was preventing the electrophile from approaching the aryl ring. Therefore, we decided to switch protecting groups from the tetrahydropyranyl ether to the much smaller methyl ether protecting group. Once again we attempted to couple the bromide (**30**) with the higher order cyanocuprate derived from 1,4-dimethoxybenzene (**35**), and this time we met with success as the desired compound (**36**) was isolated in 96 % yield based on recovered starting material. Unfortunately, the reaction only proceeded in typically 40 % conversion under a variety of conditions.



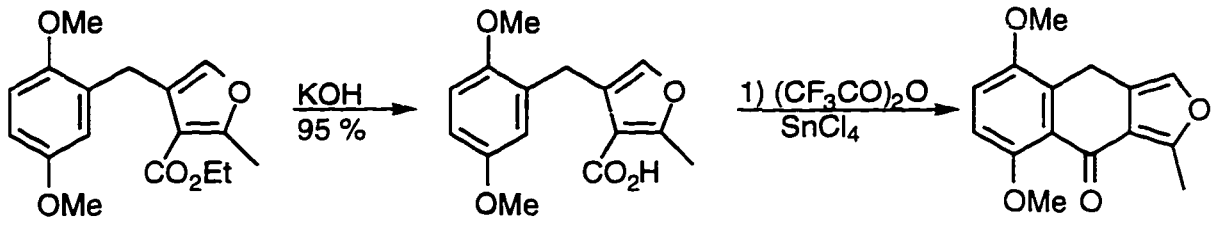
(**35**) (**30**) (**36**)

We next tried to directly convert compound (**36**) to the cyclized compound (**37**). To do this, we employed a wide variety of Friedel-Crafts conditions such as concentrated sulfuric acid and aluminum chloride. However, we were unsuccessful in all of these attempts, and we were forced to use a somewhat longer route to achieve the desired 3-methyl-(9*H*)-naphtho[2,3-*c*]furan-4-one ring system.



(**36**) (**37**)

To achieve cyclization to compound (**37**), we had to resort to a two-step procedure where we first converted the ethyl ester (**36**) to its corresponding carboxylic acid (**38**) by refluxing it in methanolic potassium hydroxide. Cyclization of the acid (**38**) was then achieved by making the mixed anhydride with trifluoroacetic anhydride and treating that compound *in situ* with tin(IV) chloride to give compound (**37**) in 50 % overall yield.[17]

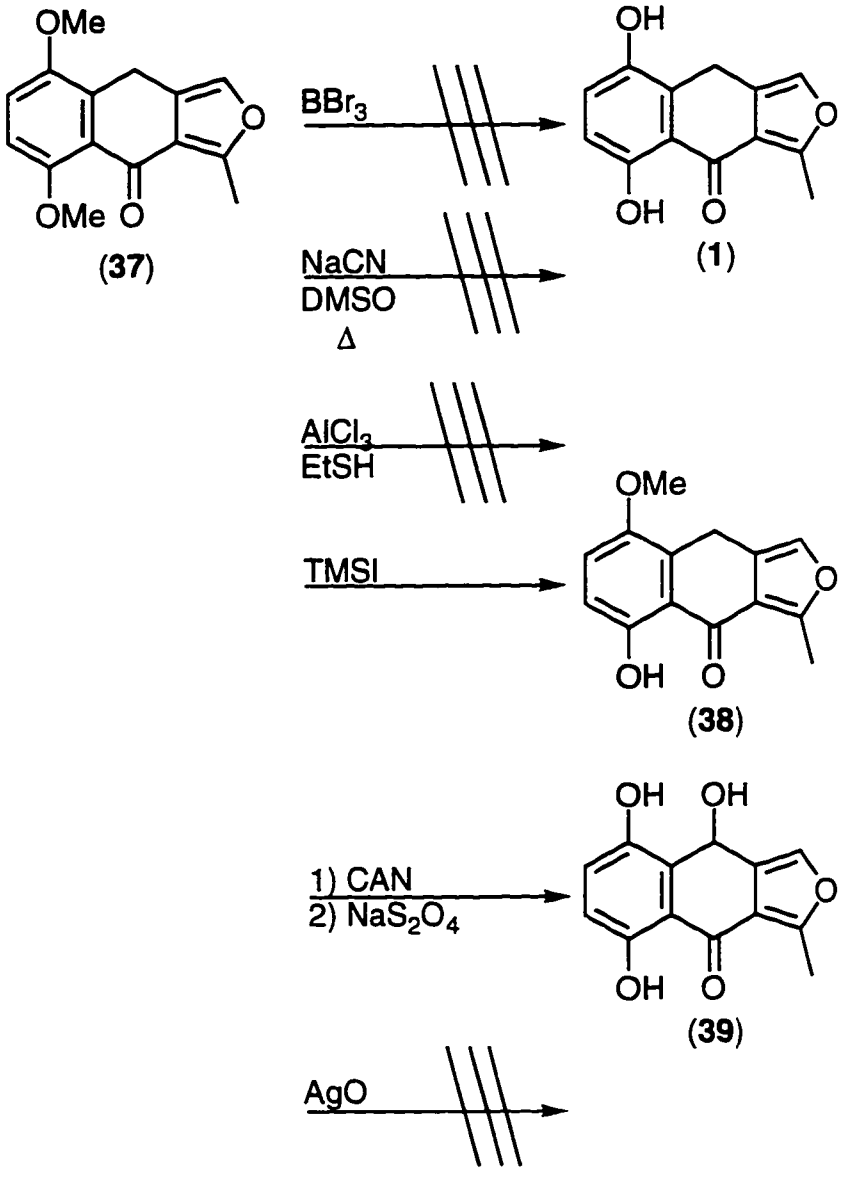


(36) (38) (37)

The last step was to remove the methoxy ethers to provide MS-444 (**1**). Unfortunately, this proved to be harder than anticipated as traditional methods[18] failed to provide any of the desired product (Scheme VII). Boron tribromide gave decomposition products as did sodium cyanide in DMSO at 135 °C. Aluminum trichloride in ethyl thiol also produced no desired product. The only reagent that did not produce decomposition products was trimethylsilyl iodide, which removed only one of the methyl ethers. A large excess of trimethylsilyl iodide did not improve the situation, but only led to decomposition of starting material. In addition, all attempts at achieving the hydroquinone through oxidation, followed by reduction, met with failure. Oxidation of the dimethyl ether with ceric(IV) ammonium nitrate followed by reduction with sodium hydrosulfite led to oxidation at the benzylic methylene. Oxidation with silver(II) oxide led to decomposition of the starting material.

At this point, we decided to report the synthetic sequence which we had devised rather than returning to the beginning and making changes. It is conceivable that the same synthesis could be done using a different protecting group on the phenols. Hopefully, these new protecting groups would be easier to remove, allowing for a successful total synthesis of MS-444 (**1**). The methoxymethyl ether would probably be the best choice for replacing the methoxy protecting groups because they are similiar in structure and easier to remove.

Scheme VIII


OMe
OMe O
(37)
BBr3
OH
OH O
(1)
NaCN
DMSO
Δ
AlCl3
EtSH
TMSI
OMe
OH O
(38)
1) CAN
2) NaS2O4
OH OH
OH O
(39)
AgO

Conclusions

We have developed a short route towards the 3-methyl-(9*H*)-naphtho[2,3-*c*]furan-4-one ring structure of MS-444 (**1**) and are very close to completing a total synthesis of that molecule. In addition, we have developed a pathway to the synthesis of a highly functionalized trisubstituted furan. With a few subtle changes in our route, such as trying a different protecting group on the hydroquinone, a complete total synthesis of MS-444 could be achieved in the future.

Experimental

Unless otherwise noted, materials were obtained from commercial suppliers and used without additional purification. Diethyl ether and tetrahydrofuran (THF) were distilled from sodium benzophenone ketyl. Benzene was distilled from lithium aluminum hydride. Toluene and methanol were distilled from sodium. Dichloromethane (CH_2Cl_2), and acetonitrile were distilled from calcium hydride. All reactions were conducted under an argon atmosphere and all extracts were dried over anhydrous sodium sulfate or anhydrous magnesium sulfate. Apparatus for experiments requiring anhydrous conditions were flame-dried under a stream of argon or dried in a 150 °C oven for 12 hours and cooled under a stream of argon. Alumina chromatography was conducted using activated neutral aluminum oxide, Brockmann I, standard grade (150 mesh), which was purchased from Aldrich Chemical Company. Silica gel chromatography (sgc) was performed on EM Science Kieselgel 60 (mesh 230-400). Thin layer chromatography (tlc) was performed using EM Science Kieselgel F_{254} prepared plates with a thickness of 0.25 mm. The solvent systems were suitable mixtures of hexanes (H) and ethyl acetate (EA) unless otherwise noted. Infrared spectra were obtained on a Perkin-Elmer 1320 spectrophotometer and are reported in cm^{-1}. Proton nuclear magnetic resonance spectra (300 MHz) were obtained using a Nicolet Magnetics Corporation NMC-1280 spectrometer. All chemical shifts are reported in δ relative to tetramethylsilane as an internal standard. Splitting patterns are designated as s (singlet), d (doublet), t (triplet), q (quartet), dd (doublet of doublets), dt (doublet of

triplets), and m (multiplet); the addition of br indicates a broadened pattern. Carbon-13 NMR spectra (75.46 MHz) were obtained on a Nicole NMC-1280 spectrometer and are reported in δ relative to $CDCl_3$ (77.00 ppm) as an internal standard. High resolution mass spectra (HRMS) were obtained on a Kratos model MS-50 spectrometer. Low resolution mass spectra (MS) were obtained on a Finnigan 4023 mass spectrometer. The purity of all title compounds was determined to be > 90 % by ^1H NMR spectral determination.

Ethyl 4-(hydroxymethyl)-2-methyl-3-furoate (29). This procedure is a slight modification of Hanson's procedure.[14] To a solution of ethyl acetoacetate (6.81 g, 52.3 mmol) in 50 mL of ethanol (200 proof) was added 1,3-dihydroxyacetone dimer (7.07 g, 39 mmol). The heterogeneous solution was then stirred for 15 minutes while the $ZnCl_2$ was being fused, to dissolve most of the 1,3-dihydroxyacetone dimer. The $ZnCl_2$ (7.12 g, 52.3 mmol) was added at room temperature, and the solution stirred for a period of one day and monitored by TLC. Generally, more $ZnCl_2$ (1-1.25 equivalents) had to be added to ensure that the reaction went to completion. The solution was then concentrated and dissolved in ether. The organic solution was washed with water and brine then dried over Na_2SO_4. Concentration provided 9.64 g (100 %) of a crude yellow liquid that was typically pure enough for immediate use. Attempts to purify by silica gel or alumina chromatography resulted in a large reduction of yield (15 %). Attempts to purify via vacuum distillation led to loss of water and formation of what was believed to be the corresponding polyester. This compound is stable for months if kept in the freezer; otherwise polymerization is bound to occur. ^1H NMR ($CDCl_3$) δ 1.35 (t, J = 7.1 Hz, 3H), 2.51 (s, 3H), 4.31 (q, J = 7.1 Hz, 2H), 4.52 (s, 2H), 7.19 (s, 1H). IR (neat) 3446, 2982, 1714, 1610, 1434, 1103, 737 cm^{-1}. MS (CI) m/z 185, 137,109. HRMS m/z calculated for $C_9H_{12}O_4$: 184.0736, measured 184.0735. ^{13}C NMR ($CDCl_3$) δ 14.3, 14.5, 55.8, 60.8, 112.8, 120.0, 138.2, 160.8, 165.3. TLC (4:1 H:EA) R_f = 0.27.

Ethyl 4-(bromomethyl)-2-methyl-3-furoate (30). To a solution of alcohol (**29**) (2.93 g, 15.9 mmol) at 0 °C in 15 mL of ethyl ether was added PBr_3 (0.76 mL, 7.95 mmol) dropwise via syringe. The solution was then stirred at 0 °C and monitored by TLC. When reaction was complete, the solution was quenched with ice, and the aqueous layer extracted twice with ether (30 mL). The combined organic layers were washed with brine and dried over Na_2SO_4. The solution was then concentrated to give 2.81 g (72 %) of a crude yellow oil that was typically pure enough for immediate use. As in the case of the corresponding alcohol (**29**), all attempts at purification met with failure. It should be noted that this compound is a powerful lachrymator and should be kept in the hood at all times. ^{1}H NMR ($CDCl_3$) δ 1.39 (t, J = 7.1 Hz, 3H), 2.55 (s, 3H), 4.34 (q, J = 7.2 Hz, 2H), 4.56 (s, 2H), 7.35 (s, 1H). IR (neat) 2982, 1715, 1567, 1465, 1380, 1297, 1101, 673 cm^{-1}. MS (CI) m/z 247, 202, 184, 167. ^{13}C NMR ($CDCl_3$) δ 14.0, 14.1, 23.0, 60.2, 111.9, 122.9, 140.2, 160.9, 163.5. TLC - not stable.

Ethyl 4-(2,5-dimethoxyphenyl)methyl-2-methyl-3-furoate (36). To a solution of 1,4-dimethoxybenzene (3.15 g, 22.8 mmol) in 50 mL of THF at 0 °C was added *n*-BuLi (22.8 mmol, 9.67 mL of a 2.36M solution in hexanes) dropwise via syringe. The solution was stirred at 0 °C for one hour. Copper(I) cyanide (1.02 g, 11.4 mmol) was added rapidly at 0 °C. The solution usually had to be warmed to room temperature for a brief period of time to ensure a homogeneous solution. After one hour, the dark green solution was cooled to -78 °C, and the ethyl 4-(bromomethyl)-2-methyl-3-furoate (**30**) (2.81 g, 11.4 mmol) was added in 10 mL of THF via cannula. The solution was allowed to warm to room temperature overnight. The anion was quenched with water, and the solution extracted with ether. The combined organic layers were washed with brine and dried over Na_2SO_4. The crude material was purified over silica gel via flash column chromatography (13:1 H:EA) to give 1.00 g of a yellow oil. A large quantity of the starting 1,4-dimethoxybenzene was also recovered. The yield based on recovered

starting material was 96 % with a conversion of 30 %. Longer reaction times resulted in no significant increase in percent conversion. ^{1}H NMR ($CDCl_3$) δ 1.25 (t, J = 7.1 Hz, 3H), 2.54 (s, 3H), 3.72 (s, 3H), 3.78 (s, 3H), 3.91 (s, 2H), 4.23 (q, J = 7.1 Hz, 2H), 6.69 - 6.81 (m, 4H). IR (neat) 2981, 1713, 1500, 1097, 942 cm^{-1}. MS (CI) m/z 305, 259, 227. HRMS m/z calculated for $C_{17}H_{20}O_5$: 304.1311, measured 304.1303. ^{13}C NMR ($CDCl_3$) δ 13.8, 14.0, 24.9, 55.1, 55.5, 59.4, 110.7, 110.8, 112.8, 116.0, 124.1, 129.6, 138.6, 151.3, 153.2, 159.9, 164.1. TLC (7:1 H:EA) R_f = 0.44.

4-(2,5-Dimethoxyphenyl)methyl-2-methyl-3-furoic acid (38). Compound (**36**) (0.210 g, 0.690 mmol) was dissolved in 5 mL of a methanol/water solution of potassium hydroxide. (The potassium hydroxide solution was prepared by adding 35 g of potassium hydroxide to 25 mL of water and then diluting to 100 mL with methanol). The reaction mixture was heated to reflux for a period of 12 hours. The solution was then acidified with 6N HCl and extracted with ether. The organic layers were combined, washed with brine and dried over $MgSO_4$. Concentration gave 0.175 g (92 %) of a white solid: mp 152-154 °C. ^{1}H NMR ($CDCl_3$) δ 2.59 (s, 3H), 3.75 (s, 3H), 3.78 (s, 3H), 3.96 (s, 2H), 6.72 - 6.82 (m, 4H). IR (film) 3048, 2917, 1676, 1504, 1233, 1116, 805 cm^{-1}. MS (CI) m/z 276, 259, 227. HRMS m/z calculated for $C_{15}H_{16}O_5$: 276.0998, measured 276.0992. ^{13}C NMR ($CDCl_3$) δ 14.6, 25.2, 55.5, 56.0, 111.4, 111.5, 112.3, 125.1, 129.6, 139.0, 151.7, 153.4, 162.0, 170.5. TLC (4:1 H:EA) R_f = 0.36.

5,8-Dimethoxy-3-methyl-(9*H*)-naphtho[2,3-*c*]furan-4-one (37). Following the procedure of Kraus,[17] the carboxylic acid (**38**) (0.617 g, 2.23 mmol) was dissolved in 10 mL of methylene chloride. The solution was cooled to 0 °C and the trifluoroacetic anhydride (0.63 mL, 4.47 mmol) was added neat via syringe. This solution was stirred for 30 minutes. The tin(IV) chloride (6.7 mmol, 0.67 mL of a 1M solution in CH_2Cl_2) was added dropwise, and the reaction monitored by TLC.

The reaction was quenched with saturated $NaHCO_3$ and extracted with CH_2Cl_2. The combined organic layers were washed with brine and dried over Na_2SO_4. The crude material was purified over silica gel via flash column chromatography (4:1 H:EA to 2:1 H:EA) to give 0.283 g (50 %) of a pale yellow solid: mp 132-134 °C. The product is somewhat sensitive and should be stored under an argon atmosphere in the freezer. ^1H NMR ($CDCl_3$) δ 2.61 (s, 3H), 3.71 (s, 3H), 3.76 (s, 2H), 3.81 (s, 3H), 6.74 (d, J = 9.0 Hz, 1H), 6.87 (d, J = 9.0 Hz, 1H), 7.12 (s, 1H). IR (film) 3102, 2915, 1653, 1559, 1471, 1253, 1080 cm^{-1}. MS (CI) m/z 259, 243. HRMS m/z calculated for $C_{15}H_{14}O_4$: 258.0892, measured 258.0895. ^{13}C NMR ($CDCl_3$) δ 13.5, 19.3, 55.4, 56.1, 110.1, 114.2, 117.8, 120.6, 122.9, 131.6, 134.5, 150.1, 154.9, 156.6, 182.2. TLC (3:1 H:EA) R_f = 0.39.

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CHAPTER 3. A SYNTHETIC APPROACH TO HALENAQUINONE

A paper to be submitted to the Journal of Organic Chemistry

George A. Kraus and John H. Malpert

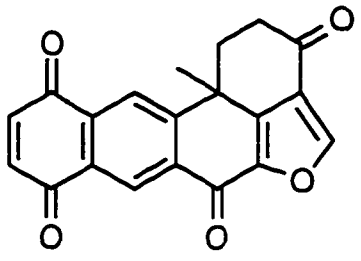
Introduction

In the last two decades discoveries in the field of marine natural products chemistry have yielded a vast array of novel secondary metabolites. Structure classes arising from a variety of biosynthetic pathways have been discovered, and many of these classes are unique to the marine environment. One class of marine metabolites that has received considerable attention from the scientific community is the one that involves the mixed biogenesis of a sesquiterpene unit with either a quinol or quinone. These marine sesquiterpenes have mainly been isolated from sea sponges, although examples have also been found in brown algae and gorgonians.

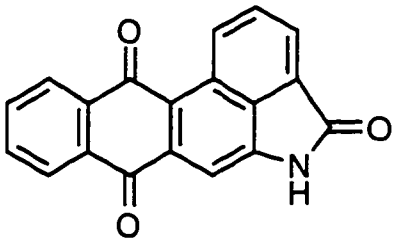
Over the past two decades, over 100 of these structures containing the quinol or quinone moiety have been reported in the literature. Unfortunately, in some cases, the absolute stereochemistry of these marine metabolites was poorly documented. This has lead to some structures being assigned a certain stereochemical structure that was not based on experimental evidence, but due to a "stereochemical bias" that was perpetuated by the previous chemical literature. Fortunately, a recent review by Capon addresses these aforementioned issues.[1]

In 1983 Clardy and co-workers isolated and characterized the structure of a new pentacyclic polyketide from tropical marine sponges.[2] They gave the name halenaquinone (**1**) to this structure, and they claimed that its pentacyclic system was the first of its kind. At the time, the closest literature analog which they could find was benzo[*cd*]naphth[2,3-*f*]indole-4,7,12(5*H*)-trione (**2**). However, they did not

define halenaquinone's absolute stereochemistry at that time. Clardy and co-workers then proceeded to test the compound for biological activity. They found that halenaquinone possessed *in vitro* antibiotic activity against *Staphylococcus aureus* and *Bacillus subtilis*.

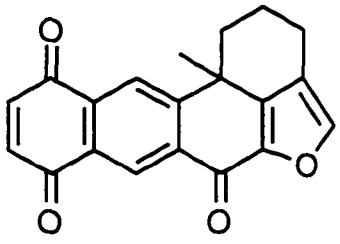


(**1**)



(**2**)

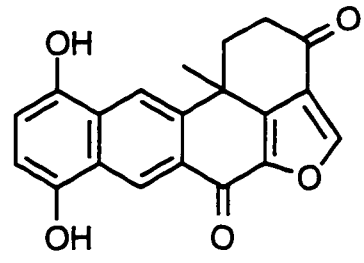
In 1985 Nakamura and co-workers isolated and characterized another bioactive metabolite from the Okinawan sea sponge *Xestospongia sapra*.[3] This structure was identical to halenaquinone (**1**) with the exception of missing a carbonyl at the 3-position. Once again, as in the case of halenaquinone (**1**), the absolute stereochemistry was left undefined. They named this compound xestoquinone (**3**) and proceeded to study its biological activity. They found that xestoquinone (**3**) showed powerful cardiotonic activity and showed a marked inotropic action. It also caused a concentration-dependent inhibitory effect on the Na,K-ATPase isolated from pig cerebral cortex. Xestoquinone was the first example of a marine natural product that showed these aforementioned characteristics.



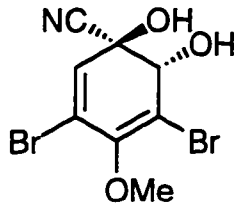
(**3**)

In 1992 researchers at the University of California, Santa Cruz working jointly with workers in private industry at Syntex Research, studied the biological effects of halenaquinone (**1**), xestoquinone (**3**) and several other non-natural analogs.[4] Specifically, they were studying the effects of these compounds as protein tyrosine kinase inhibitors. Enhanced protein tyrosine kinase (PTK) activity has been linked with proliferative diseases, such as cancer and psoriasis.[5] Both the receptor types and cytoplasmic types of PTKs have been associated with cancer found in humans. This family of enzymes is also involved in the regulation of both cellular growth and signaling. Therefore, it is believed that compounds which inhibit PTK activity could be developed into new chemotherapeutic agents.

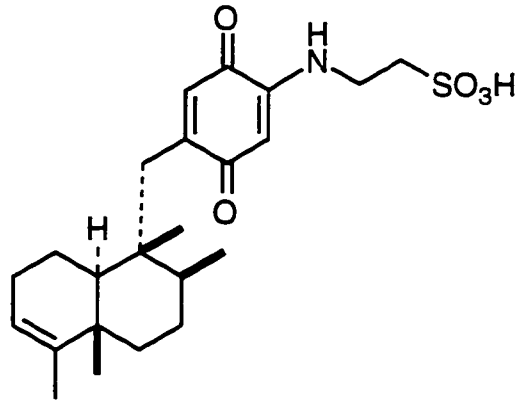
These researchers examined the effects halenaquinone (**1**) and its related analogs had on the protein tyrosine kinase activity of $pp60^{v\text{-}src}$, the transforming gene product of the Rous sarcoma virus. Halenaquinone (**1**) proved to be a potent, irreversible inhibitor of the aforementioned enzyme. Halenaquinol (**4**), the corresponding hydroquinone, was also as potent as its parent compound. The IC_{50} of halenaquinone (**1**) was found to be 1.5 μM, while the IC_{50} of halenaquinol (**4**) was found to be 0.55 μM. These two compounds (**1**) and (**4**) are among some of the most potent kinase inhibitors reported to date. In fact only two other compounds are known to inhibit PTK activity, and they are aeroplysinin (**5**), and melemeleone (**6**).[4] Surprisingly, xestoquinone (**3**) was considerably less active than the other two compounds (**1**) and (**4**). In addition halenaquinone (**1**) also inhibited the ligand-stimulated tyrosine kinase activity of the human epidermal growth factor receptor with an IC_{50} of about 19 μM.



(4)



(5)



(6)

In addition to determining the biological activity of these halenaquinone analogs, these California researchers also synthesized several quinone analogs to determine which functional groups were needed to produce PTK inhibition. They found that replacing the oxygens of the napthoquinone with chlorines completely destroyed any inhibitory effects. They also concluded that the furan ring moiety was essential to inhibition as replacement of it with a benzene ring negated inhibition. They concluded that since halenaquinone (**1**) is a potentially good Michael acceptor, attack by nucleophiles at crucial positions of its structure may be what causes the anti-proliferative activity. This theory was supported by following work, although the authors admit that the details are still a little sketchy.[4,5]

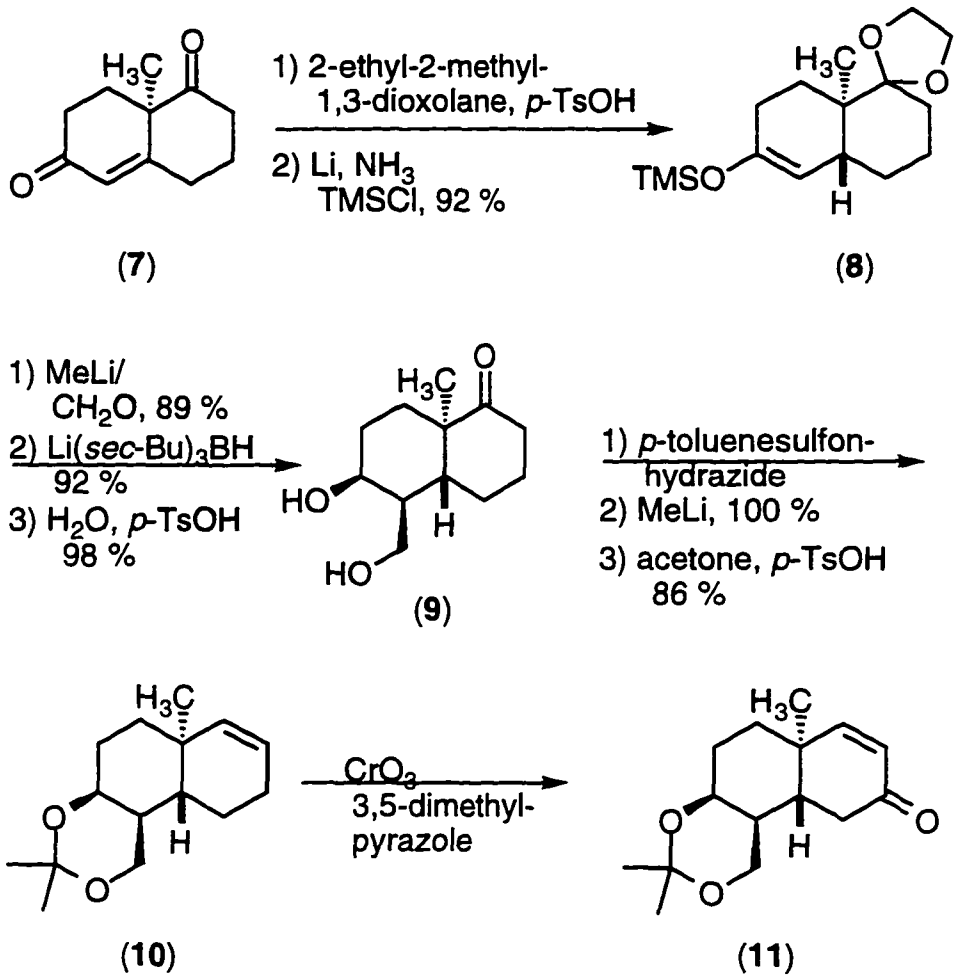
In 1993, Tsuji and co-workers at Hokkaido University in Japan discovered that halenaquinone (**1**) and xestoquinone (**3**) were potent inhibitors of Topoisomerase I purified from the nuclei of the mouse leukemic cells L1210.[6] Topoisomerase I and Topoisomerase II are important targets for antitumor agents. Both compounds (**1**) and (**3**) were also found to be cytotoxic to several different types of leukemic cells.

Although halenaquinone (**1**) was originally characterized in 1983, its absolute stereochemistry was not assigned until 1988.[7] It was at this time when Harada and co-workers synthesized (+)-halenaquinone and (+)-halenaquinol, and they determined that the absolute stereochemistry at the lone chiral center was (S). Since that time, only one other synthesis of halenaquinone (**1**) has been totally completed and that was by Shibasaki and co-workers.[8] In addition, another approach to the halenaquinone ring system has appeared by Keay and co-workers.[9] However, they did not successfully finish the whole molecule.

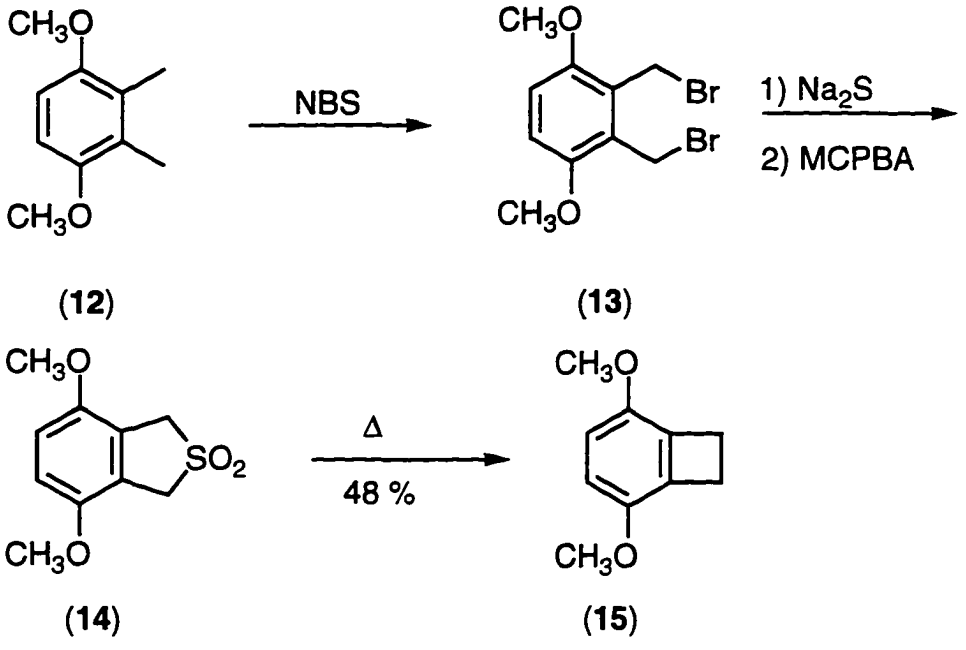
Harada began his synthesis (Scheme I) with optically pure (8a,R)-(-) Wieland-Miescher ketone (**7**).[7] Using known procedures, he selectively protected the non-allylic ketone and then reduced the enone, trapping the corresponding enolate with trimethylsilyl chloride in 92 % yield to give (**8**). With compound (**8**), he formed the appropriate enolate and hydroxymethylated it by treating it with formaldehyde. After selectively reducing the ketone to the axial alcohol, he removed the acetal protecting group in excellent yield to give (**9**). Transformation of the ketone (**9**) to the hydrazide and elimination gave the corresponding alkene in quantitative yield. The diol was then protected as its 1,3-dioxane to give (**10**) in 86 % yield. Compound (**10**) was then oxidized at the allylic position to give enone (**11**) in 63 % yield.

The next phase of the synthesis called for the synthesis of a benzocyclobutene, which would eventually be used in a thermal [4+2] cycloaddition. Harada (Scheme II) began with 2,3-dimethyl-1,4-dimethoxybenzene (**12**) and dibrominated at the benzylic position using NBS to give (**13**). The dibromo compound (**13**) was then treated with sodium sulfide to give the corresponding cyclic sulfide which was oxidized to the sulfone (**14**). Thermolysis of compound (**14**) gave the desired benzocyclobutene (**15**) in 48 % yield.

Scheme I


H3C
O
O
1) 2-ethyl-2-methyl-
1,3-dioxolane, p-TsOH
2) Li, NH3
TMSCl, 92 %
TMSO
H
(7)
(8)
1) MeLi/
CH2O, 89 %
2) Li(sec-Bu)3BH
92 %
3) H2O, p-TsOH
98 %
HO
HO
(9)
1) p-toluenesulfon-
hydrazide
2) MeLi, 100 %
3) acetone, p-TsOH
86 %
CrO3
3,5-dimethyl-
pyrazole
(10)
(11)

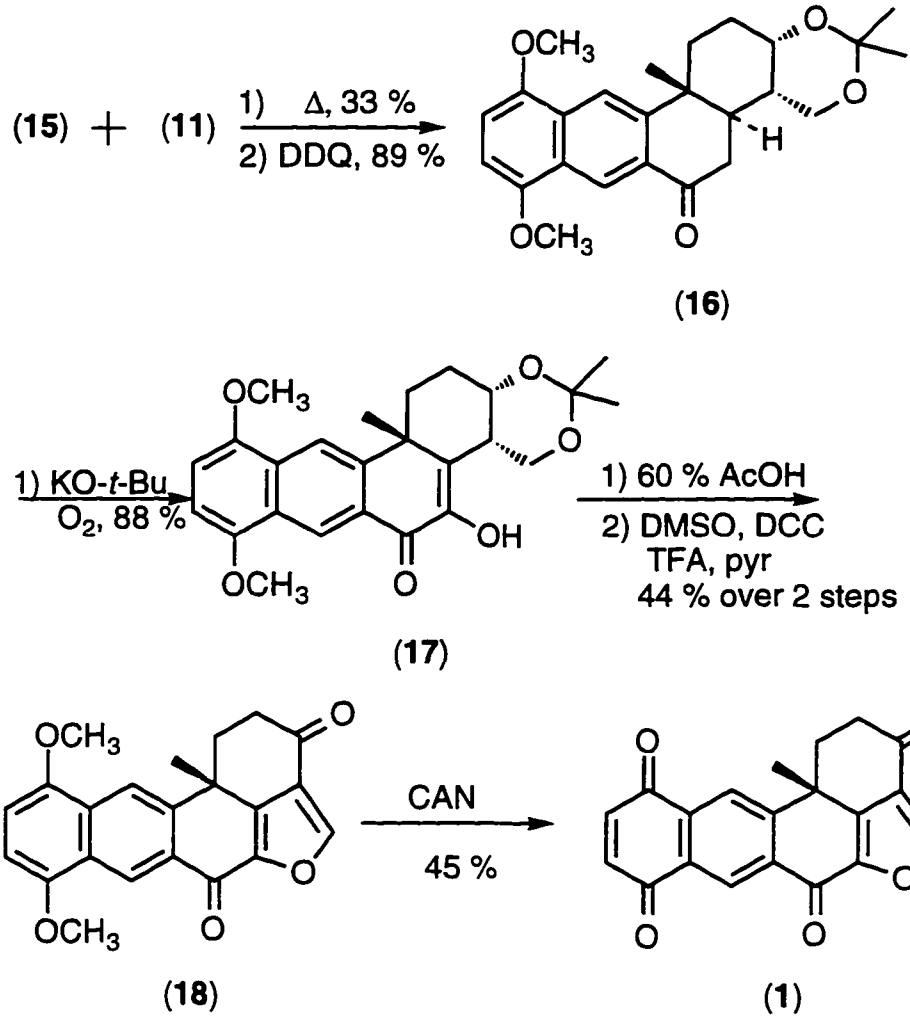
Scheme II



In Scheme III, Harada combines the benzocyclobutene (**15**) and the enone (**11**), which were made previously in Schemes I and II, and heats them together to form the cycloadduct in a disappointing 33 % yield. The cycloadduct was then aromatized to the naphthalene (**16**) with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) in 89 % yield. Treatment of compound (**16**) with base and then bubbling oxygen through the solution gave the dione (**17**) in excellent yield. The 1,3-dioxane was then deprotected, and the resulting triol was oxidized and cyclized to the pentacyclic furan (**18**) in 44 % yield over two steps. Oxidation of compound (**18**) gave halenaquinone (**1**) in 45 % yield.

Although the synthesis of Harada's was a terrific achievement, a couple of improvements could be made. The first disappointment was the low yield of the [4+2] cycloaddition (33 %), causing a great deal of starting material to be lost. The second criticism of Harada's synthesis was that he put in quite a few chiral centers only to remove them later in the synthesis, thus lowering the efficiency of the synthetic route. However, his synthesis was the first, and nobody would match his accomplishment for another eight years.

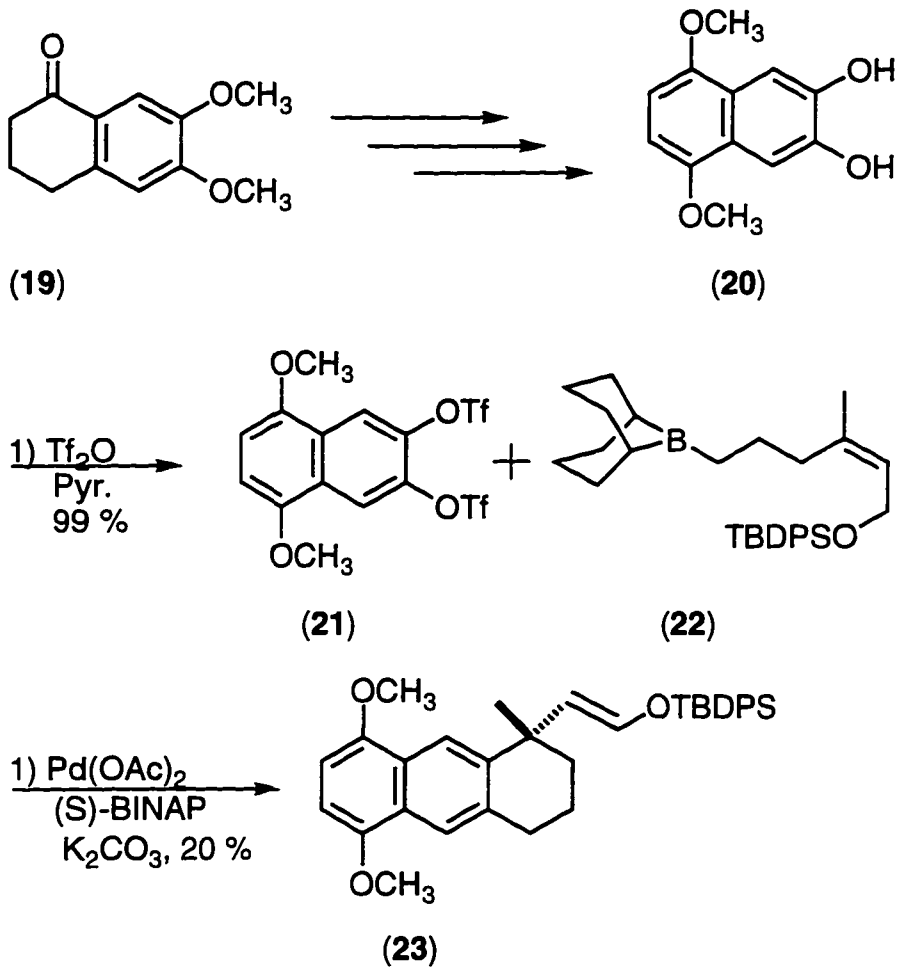
Scheme III



The second total synthesis of halenaquinone (**1**) was done in 1996 by Shibasaki,[8] who used a novel cascade Suzuki cross-coupling and asymmetric Heck reaction as his key step (Scheme IV). Shibasaki began his synthesis with the commercially available 6,7-dimethoxy-1-tetralone (**19**), which he converted to compound (**20**) in a series of five protection and deprotection reactions in 58 % yield over the five steps. Treatment of compound (**20**) with triflic anhydride and pyridine produced the triflate (**21**) in near quantitative yield. The ditriflate (**21**) was then subjected to the alkylborane (**22**), which had been synthesized in several

steps via known procedures, under palladium-catalyzed conditions. The ditriflate (**21**) underwent Suzuki coupling and then cyclized via an asymmetric Heck reaction with 85 % ee in 20 % yield. The low yield was disappointing, but the cascade of reactions was impressive nonetheless.

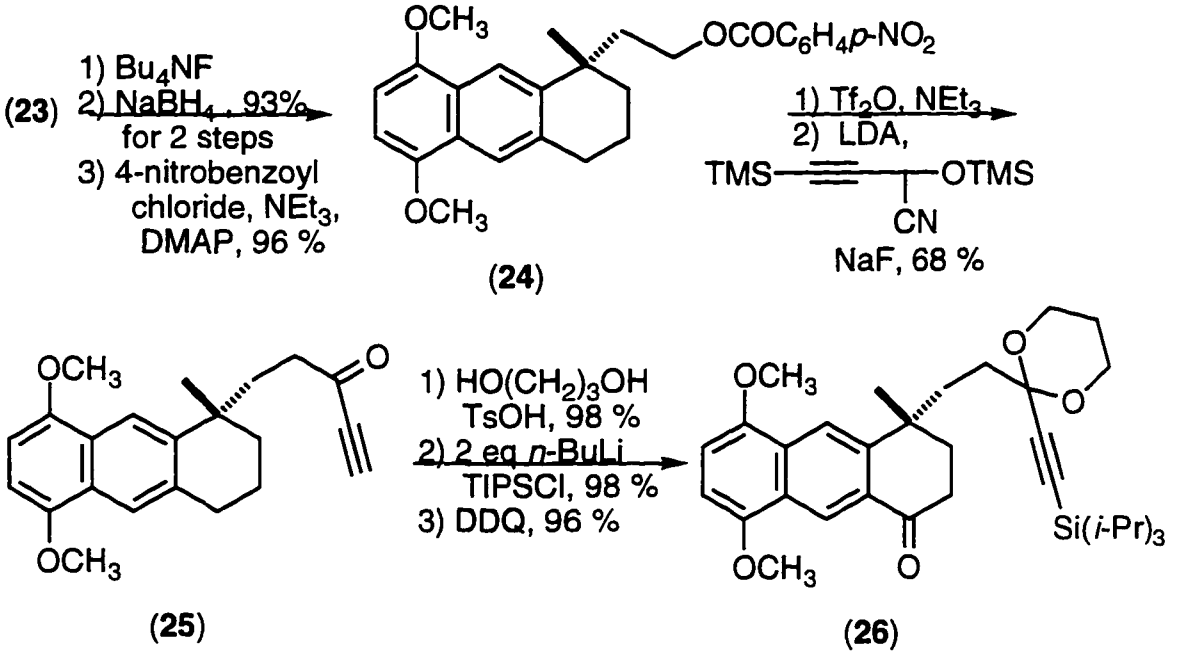
Scheme IV



A longer six step sequence from compound (**20**) to compound (**23**) was also devised. This involved protecting one of the phenols, converting the other to a triflate, and proceeding with the Suzuki coupling. The phenol was then deprotected, converted to a triflate, and then subjected to the conditions of the asymmetric Heck reaction. This step-wise pathway led to an overall 87 % ee in 29 % yield.

Having developed a pathway to an intermediate which contained the only chiral center of halenaquinone (**1**), Shibasaki went about finishing the pentacyclic skeleton. He deprotected the silyl enol ether (Scheme V) and reduced the corresponding aldehyde with sodium borohydride in 93 % yield over two steps. The alcohol was then converted to the *p*-nitrobenzyl ester to give compound (**24**) in 96 % yield. He then converted the *p*-nitrobenzyl ester into a triflate and reacted that triflate with an acyl anion equivalent to give compound (**25**) in 68 % yield. He then proceeded to protect the ketone and the alkyne in excellent yields. Benzylic oxidation with DDQ gave him the tricyclic ketone (**26**) in 96 % yield.

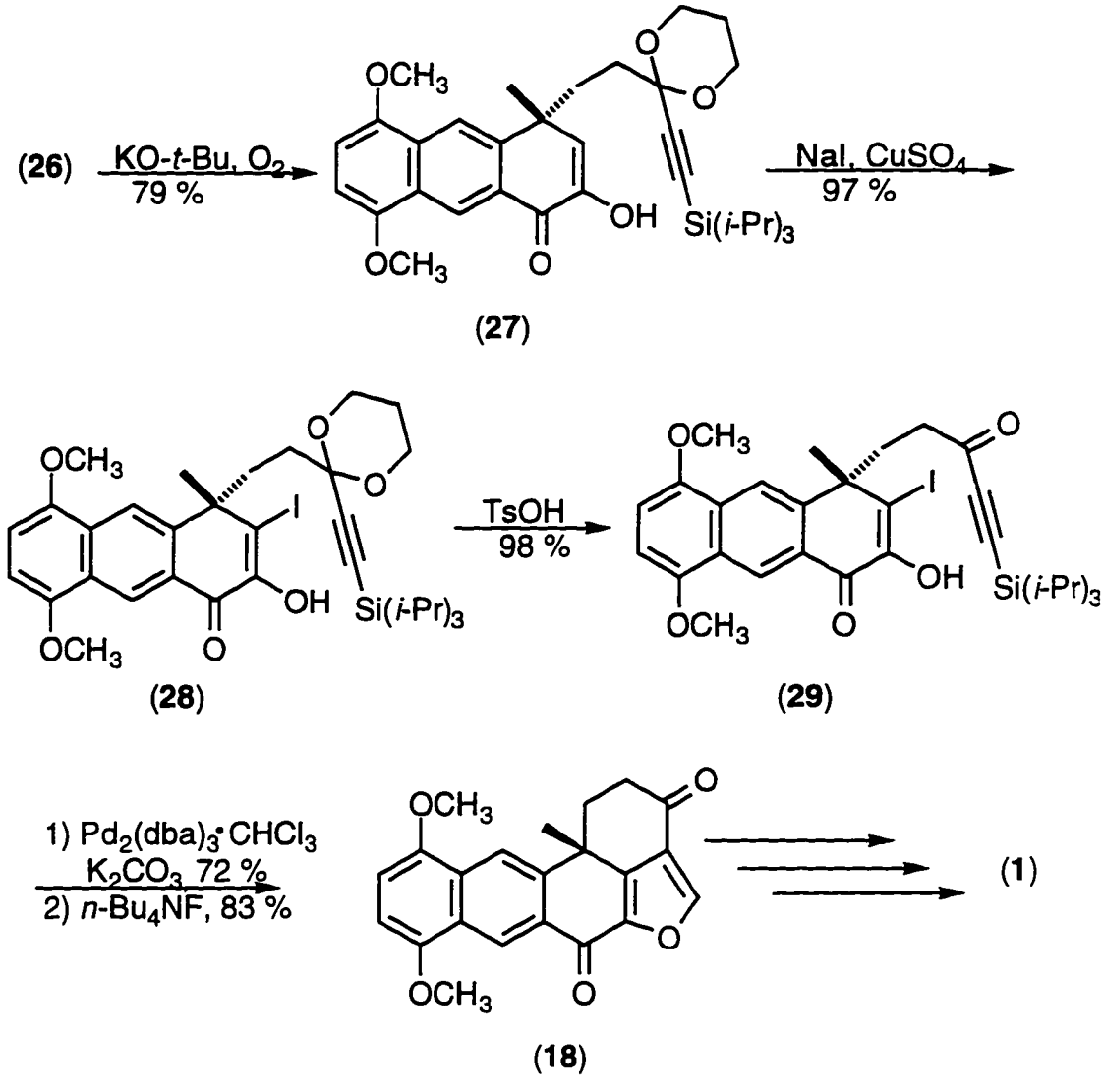
Scheme V



With compound (**26**) in hand, Shibasaki needed to introduce an oxygen moiety alpha to the benzylic carbonyl and then cyclize to form the furan ring. Treating compound (**26**) with potassium *tert*-butoxide and maintaining an oxygen atmosphere, he was able to produce the dione (**27**) in 79 % yield. The dione was converted to the vinyl iodide (**28**) by exposing it to an excess of sodium iodide and copper(II) sulfate. The cyclic acetal protecting group was then removed in almost quantitative yield to give the compound (**29**), which was poised for cyclization to

the furan ring moiety. Treatment of compound (**29**) with a catalytic amount of palladium closed both rings to afford the pentacyclic structure of halenaquinone (**1**) in 72 % yield. Removal of the triisopropylsilyl protecting group on the furan ring was achieved by treating with tetrabutylammonium fluoride in 83 % yield to afford compound (**18**), which had been previously synthesized by Harada and co-workers.

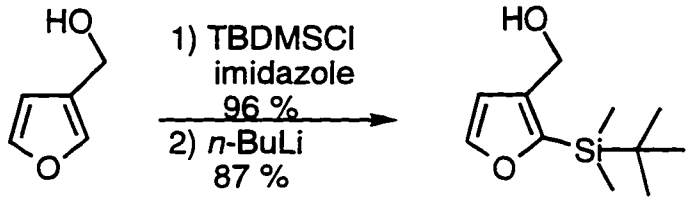
Scheme VI



The synthesis by Shibasaki, like the synthesis of Harada, had the drawback of its key step, the cascade Suzuki cross-coupling and asymmetric Heck reaction [compound (**21**) to compound (**23**) in Scheme IV], suffering a low yield. However, the synthesis of Shibasaki had the advantage of being more efficient in that no extra chiral centers were created at any point.

The final approach that will be presented is an approach by Keay and co-workers at the University of Calgary.[9] Keay's key step is an intramolecular palladium-catalyzed cyclization. Keay begins his synthesis (Scheme VII) with the readily available 3-(hydroxymethyl)furan (**30**). He protects the alcohol with a *tert*-butyldimethylsilyl protecting group in excellent yield. Treatment of the protected alcohol with *n*-BuLi/HMPA in THF caused 1,4-silyl migration of the silyl protecting group to the 2-position of the furan, providing compound (**31**) in 87 % yield.

Scheme VII

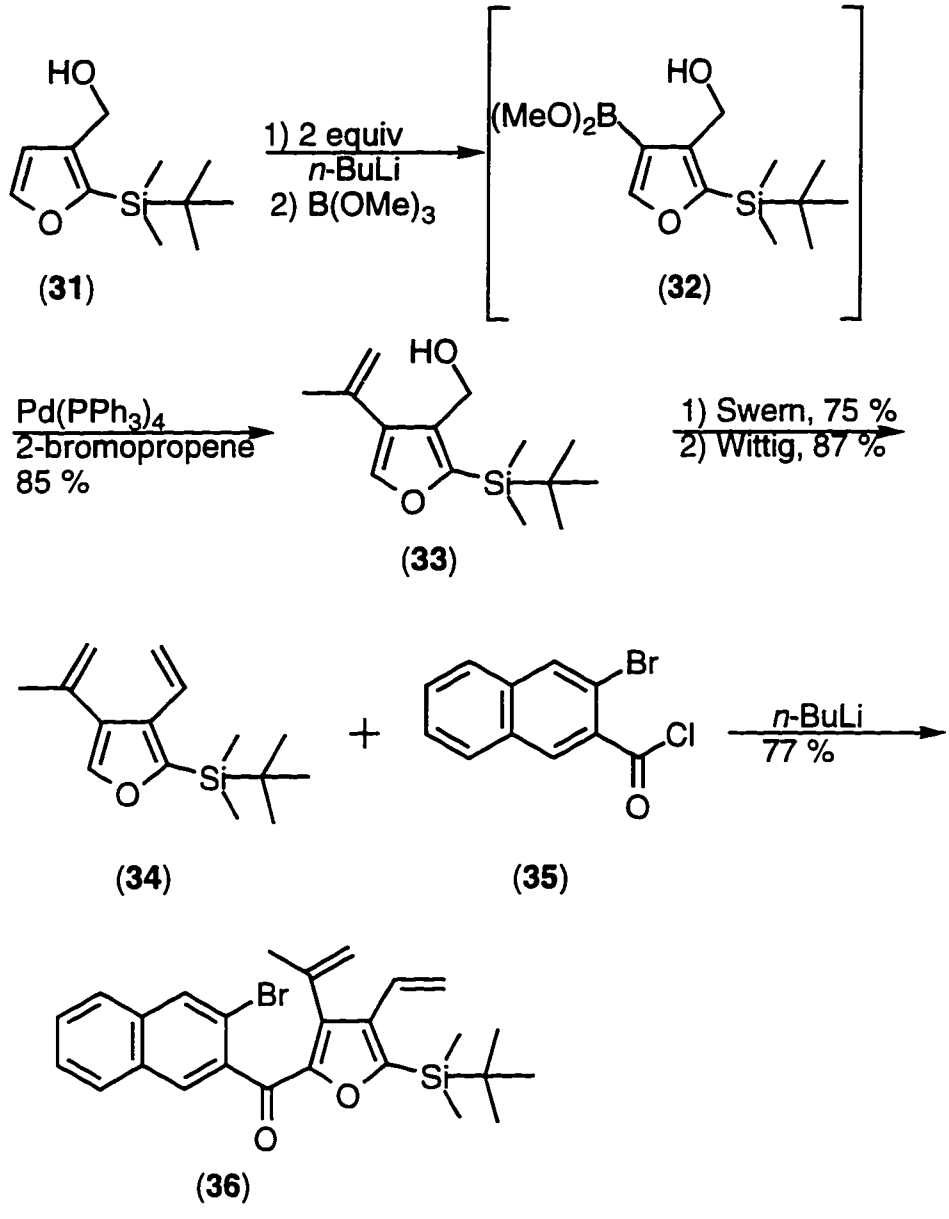


(**30**) (**31**)

Keay then modified the Suzuki coupling reaction (Scheme VIII). He first treated compound (**31**) with two equivalents of *n*-BuLi to form the anion at the 4-position of the furan ring. Quenching the dianion with trimethylborate gave compound (**32**), which was not isolated but instead used *in situ*. After ensuring that the anion was completely quenched by stirring for one hour, 2-bromopropene was added along with a catalytic amount of tetrakis(triphenylphosphine)palladium(0) to give an 85 % yield of the desired furan (**33**). This furan was then subjected to a

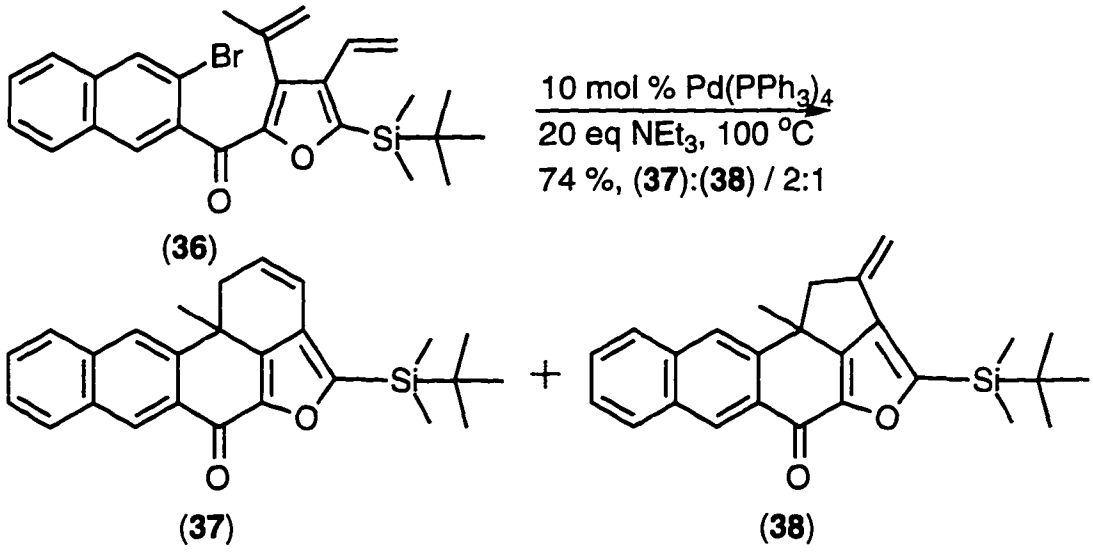
Swern oxidation to give the aldehyde in 75 % yield, and that aldehyde was changed to the corresponding alkene via a Wittig reaction to give compound (**34**) in 87 % yield. The furan (**34**) was then lithiated and quenched with the acid chloride (**35**) to produce the desired ketone (**36**) in 77 % yield.

Scheme VIII



Keay was now ready to attempt his key intramolecular palladium-catalyzed cyclization. Treating compound (**36**) (Scheme IX) with 10 mol percent of $Pd(PPh_3)_4$ cyclized the two six-membered rings to form compound (**37**). Unfortunately, compound (**38**) was also produced in a significant amount. Overall, the two products were formed in 74 % yield with the desired compound (**37**) favored by a two to one margin.

Scheme IX



(**37**) (**38**)

Although this cyclization is a very novel concept, Keay still has a ways to go before the synthesis of halenaquinone (**1**) is complete. First of all, the correct 1,4-dimethoxynaphthalene unit analogous to compound (**35**) must be synthesized. The starting material for such a compound is not very readily available, and therefore would have to be synthesized from scratch. Another problem that Keay might face is the lack of selectivity for any reaction done on the double bond in compound (**37**). Trying to install a ketone from this moiety would more than likely produce a mixture of isomers.

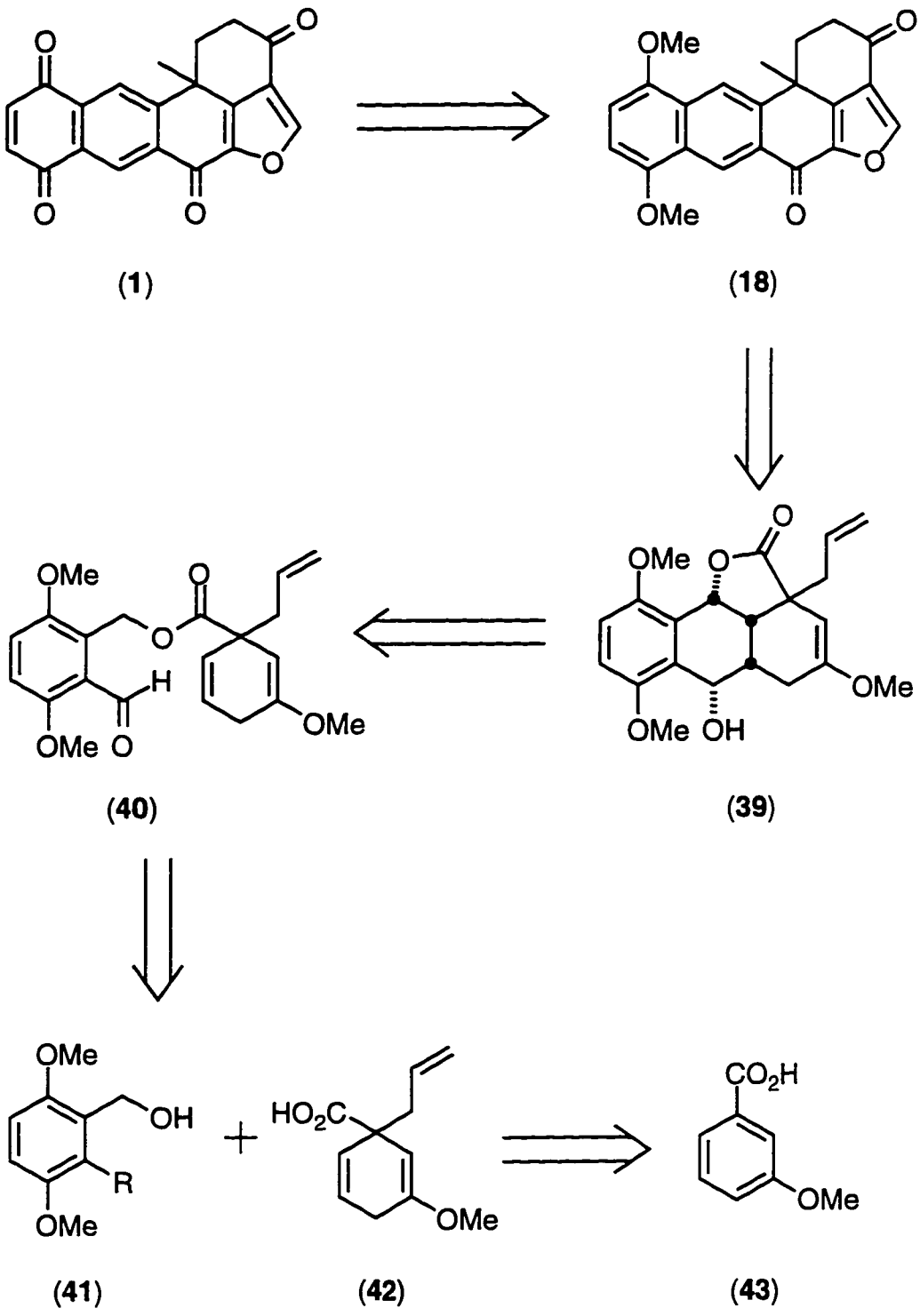
Results and Discussion

We became interested in halenaquinone (**1**) because only one total synthesis of the molecule had been reported at the time we initiated work on the

project. That synthesis was done by Harada[7] and involved a very low yielding thermal [4+2] cycloaddition as its key step. We hoped to design a more efficient synthesis that improved on this low overall yield. Since that time, another synthesis of halenaquinone (**1**) has been completed.[8] However, like the synthesis done by Harada, the overall efficiency is not all that impressive due to a low yielding (20 %) key step. Continuing in the study of tandem photoenolization/[4+2] cycloaddition reactions that has been well-documented in our group,[10,11] we set off to find a new and improved pathway to halenaquinone.

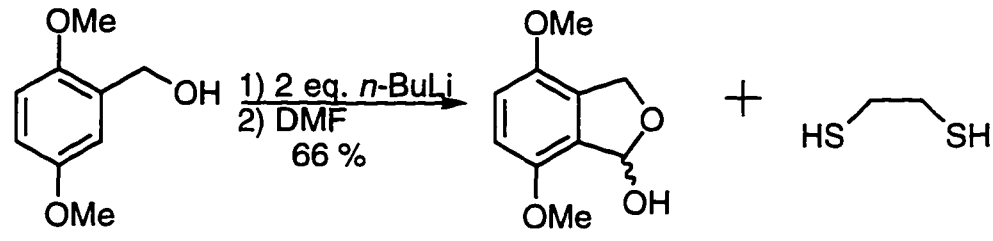
Our original retrosynthetic analysis is shown in Scheme X. We envisioned that halenaquinone (**1**) could come from a precursor such as (**39**). The naphthalene ring moiety could be made by elimination of the benzylic alcohol and cleavage of the lactone oxygen. The allyl group on compound (**39**) would serve as a functional handle for completing the fourth and fifth rings. The lactone moiety would eventually be reduced all the way down to provide the methyl group of halenaquinone (**1**). In addition, the methoxy enol ether would serve as a functional handle for installing the furan ring. We proposed that the precursor (**39**) would be made via a tandem photoenolization/[4+2] cycloaddition reaction done on an intermediate such as compound (**40**). The ester (**40**) would be made via condensation of an appropriately functionalized 2,5-dimethoxybenzyl alcohol (**41**) and the corresponding carboxylic acid (**42**). The alcohol (**41**) would come from quenching the anion of the readily available 2,5-dimethoxybenzyl alcohol with an appropriate electrophile. On the other hand, generation of the cyclohexadiene compound (**42**) would be accomplished by performing a Birch reduction on *m*-anisic acid (**43**) and alkylating the resulting anion with allyl iodide, installing the only quaternary center in halenaquinone (**1**) in the very first step.

Scheme X

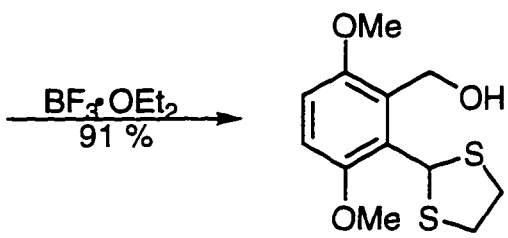

O
O
O
O
O
OMe
OMe
O
O
O
(1)
(18)
OMe
O
H
OMe
O
OMe
O
O
OMe
OMe
OH
OMe
(40)
(39)
OMe
OH
R
OMe
HO2C
OMe
CO2H
OMe
(41)
(42)
(43)

We began our synthesis of halenaquinone (**1**) (Scheme XI) by subjecting 2,5-dimethoxybenzyl alcohol (**44**) to two equivalents of *n*-BuLi and quenching the resulting dianion with *N,N*-dimethylformamide to form the hemiacetal (**45**) in 66 % yield. Metallation occurs exclusively at the 6-position due to the directing effects of the neighboring benzyl alcohol.[12] The aldehyde was then protected as a thioketal by treating compound (**45**) with 1,2-ethanedithiol (**46**) and a catalytic amount of boron trifluoride diethyl etherate to provide compound (**47**) in 91 % yield.

Scheme XI

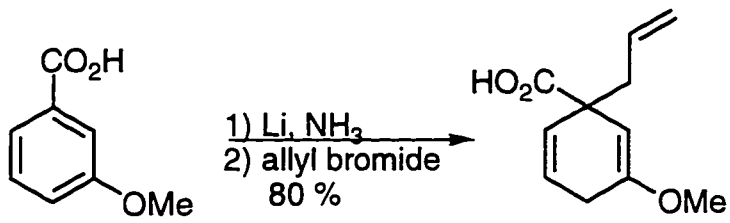


(**44**) (**45**) (**46**)



(**47**)

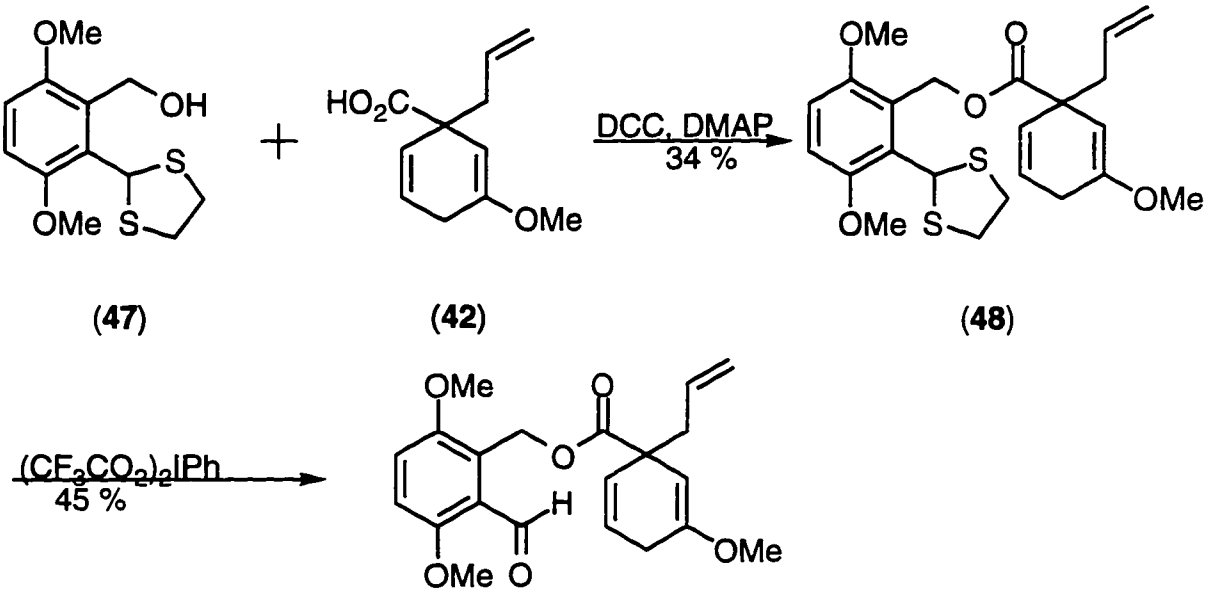
The other half of the molecule was prepared by subjecting *m*-anisic acid (**43**) to the conditions of the Birch reduction and quenching the resultant anion with allyl bromide to afford compound (**42**) in 80 % yield.[13]



(**43**) (**42**)

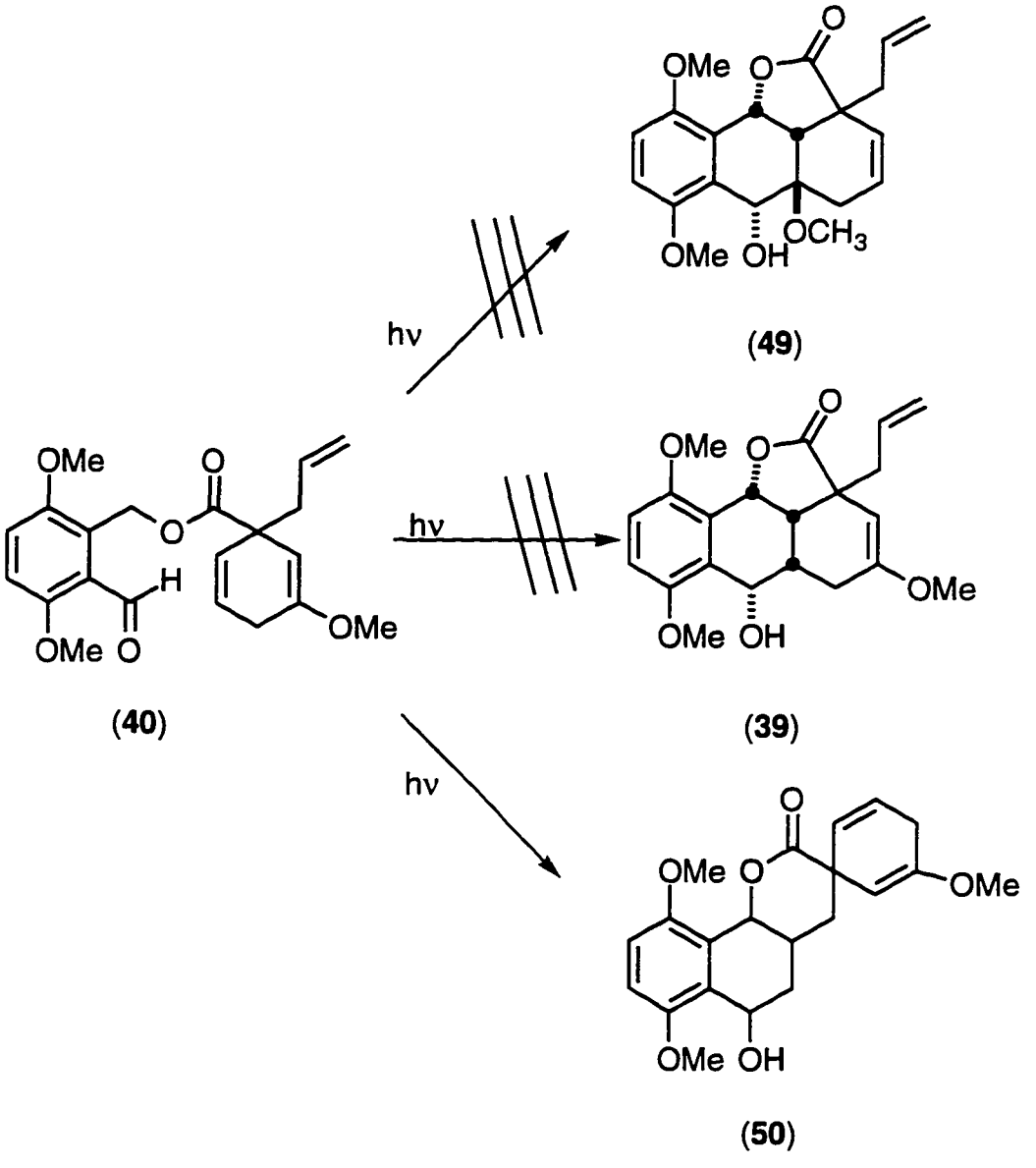
With the two products (**42**) and (**47**) in hand, it was now time to condense them into the corresponding ester. This was done (Scheme XII) by treating a mixture of the two with 1,3-dicyclohexylcarbodiimide (DCC) and a catalytic amount of 4-dimethylaminopyridine (DMAP) to give compound (**48**) in 34 % yield. Naturally, we were disappointed in the low yield, but we more interested in seeing whether or not our key photolysis reaction would work. Therefore, no attempt to improve the yield was ever made. The last step before the photolysis involved removing the thioketal protecting group. A variety of conditions were tried, and the condition that worked the best was treating compound (**48**) with [bis(trifluoroacetoxy)iodo]benzene in a solution of aqueous acetonitrile. This gave the corresponding aldehyde (**40**) in 45 % yield.

Scheme XII



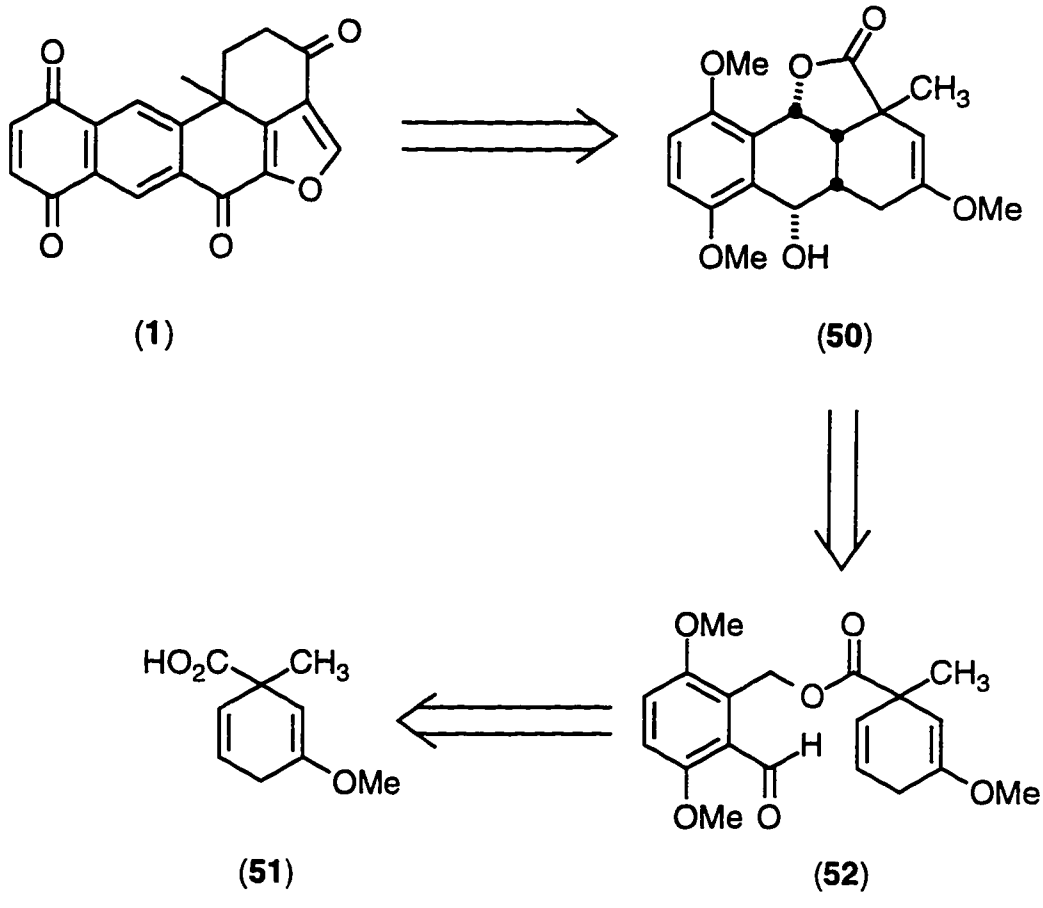
The next step was the key photolysis reaction. At the time, we were very curious to see which double bond would react with the diene. Compound (**40**) had the possibility of cyclizing three different ways (Scheme XIII). The first way, which we thought was unlikely due to steric considerations, would be to cyclize onto the

Scheme XIII


OMe
O
H
OMe
O
O
OMe
hν
(40)
OMe
O
OMe
OH
OCH3
(49)
OMe
O
OMe
OMe
OH
(39)
hν
OMe
O
OMe
OMe
OH
(50)

double bond which contained the methoxy enol ether moiety to give compound (**49**). The second double bond which could react, and the one that we hoped would react, was the unsubstituted double bond on the cyclohexane ring. The compound that would have been formed via this pathway was (**39**). The final pathway would involve the diene reacting with the double bond on the allyl substituent to give compound (**50**). Upon doing the reaction, we were disappointed to find that cyclization occurred via this final pathway.

Scheme XIV



(**1**) (**50**)

(**51**) (**52**)

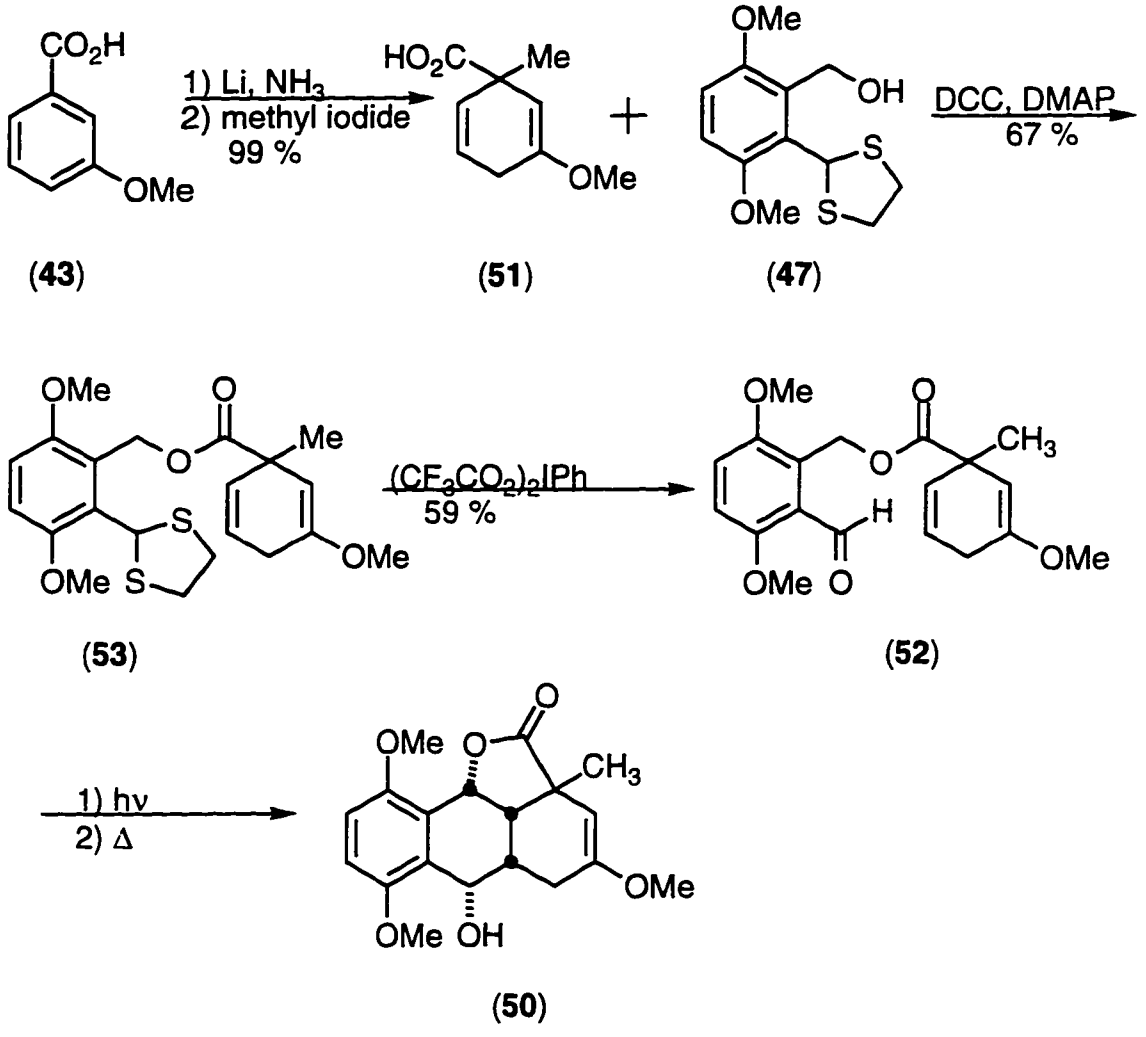
At this point we still felt that our original route could be used with just a few modifications. We went back to the beginning and changed the allyl group, since it was causing the problems, to a methyl group (Scheme XIV). Using the same conditions as before, a Birch reduction of *m*-anisic acid (**43**) and quenching with

methyl iodide would produce the carboxylic acid (**51**). The acid could then be converted to the ester (**52**), which upon subjection to light should give the intermediate (**50**). Compound (**50**) could then be converted to halenaquinone (**1**) by elimination of the benzylic alcohol and ester to give the naphthalene ring system. The lactone moiety would then serve as a functional handle for completion of the fourth and fifth rings.

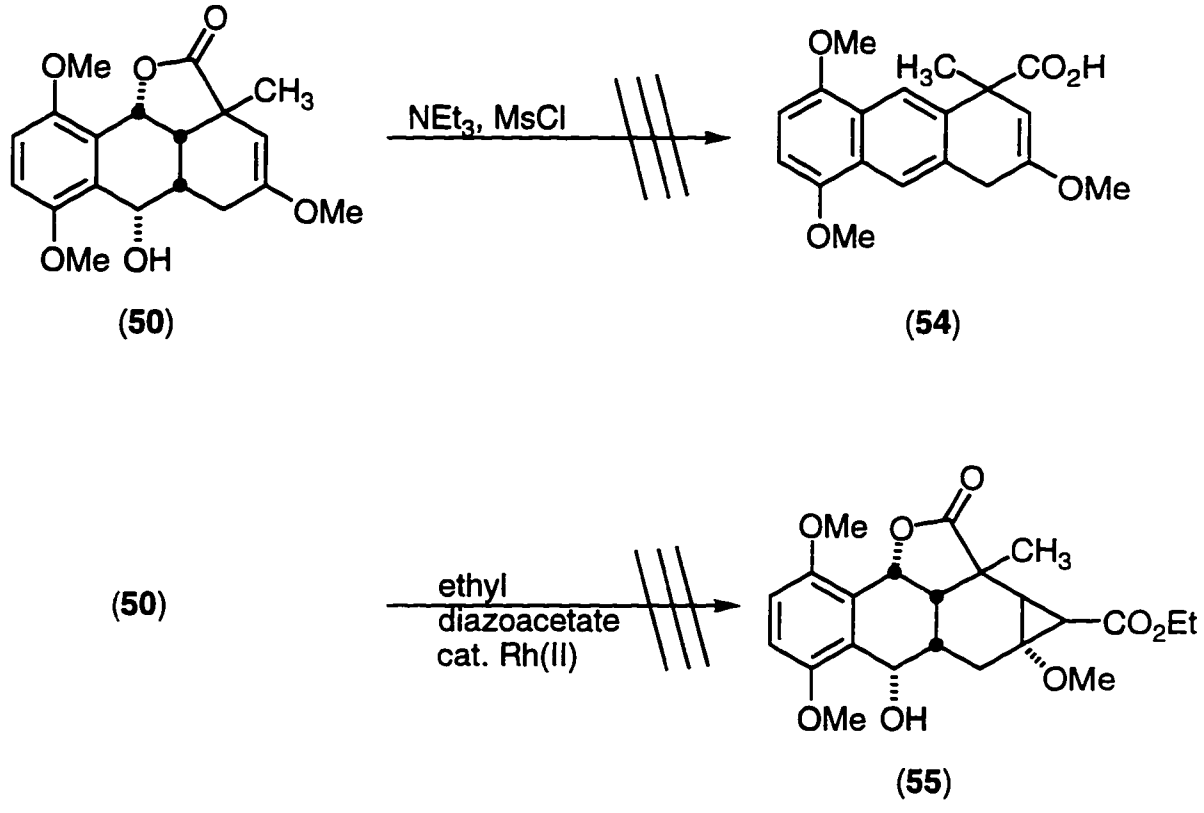
The original pathway was followed exactly as before with the exception that the allyl group was substituted by a methyl group. Birch reduction of *m*-anisic acid, followed by quenching with methyl iodide, produced the carboxylic acid (**51**) in near quantitative yield (Scheme XV). Using the same conditions as before, the acid (**51**) was esterified to provide compound (**53**) in 67 % yield. This was a significant increase (34 % to 67 %) from the other version, and much of it is due to the lack of steric hindrance of the methyl group, making attack at the carboxylic acid much easier for the nucleophile. Compound (**53**) was then deprotected in 59 % yield to provide the aldehyde (**52**). This aldehyde was then photolyzed and heated to form what we at first thought was compound (**50**). It might be noted that the stereochemical assignments were made based on previous work done in our group.[10a]

Taking compound (**50**), we then tried several experiments in which we attempted to form the naphthalene ring. We assumed that if we could eliminate the alcohol, the lactone ring would open up as well (Scheme XVI). However, several types of dehydration conditions failed to produce any type of new naphthalene (**54**) or any type of new alkene for that matter. We then tried to form a cyclopropane ring on the enol ether double bond. A compound such as (**55**) could be used to form the furan moiety. However, we were unable to successfully complete any type of cyclopropanation reaction. The reasons for these failures would become clearer later on when we discovered the true structure for compound (**50**).

Scheme XV


CO2H
OMe
1) Li, NH3
2) methyl iodide
99 %
HO2C
Me
OMe
OMe
OH
S
OMe S
DCC, DMAP
67 %
(43)
(51)
(47)
OMe
O
Me
O
S
OMe S
OMe
(CF3CO2)2IPh
59 %
OMe
O
CH3
O
H
OMe O
OMe
(53)
(52)
1) hν
2) Δ
OMe
O
O
CH3
OMe
OMe OH
(50)

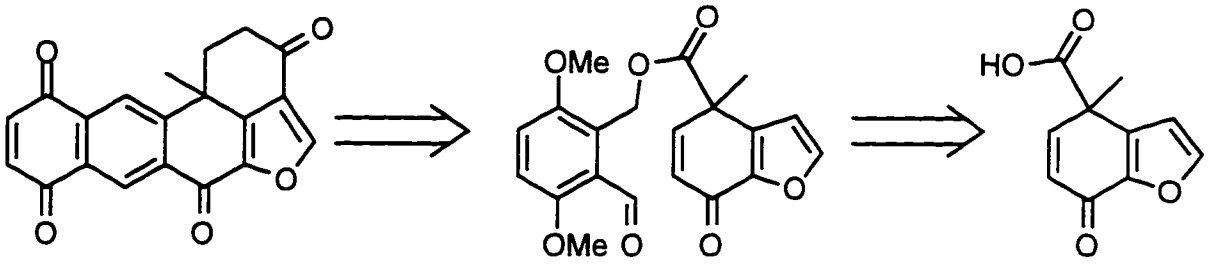
Scheme XVI



(50) (54)

(50) (55)

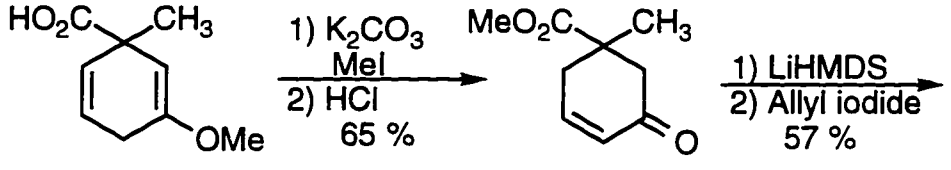
At the time, we theorized that the molecule (**50**) must have been assuming some type of unexpected conformation that was prohibiting the alcohol from eliminating. We next set out to design a system that would place a carbonyl alpha to the hydrogen that needed to be eliminated. This carbonyl would hopefully promote dehydration of that alcohol. We also decided that we would try to make our approach more convergent by installing the furan ring at the beginning of the synthesis. The retrosynthetic analysis called for a precursor like compound (**57**), which could be esterified to the intermediate (**56**). Photolysis of (**56**) would then lead to the type of precursor which could be dehydrated easily.



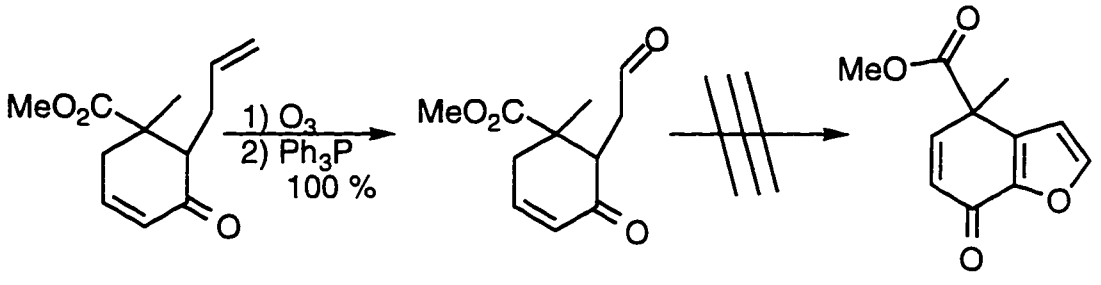
(**1**) (**56**) (**57**)

We then set out to make the carboxylic acid (**57**) (Scheme XVII). We began by taking the carboxylic acid (**51**), esterifying it, and hydrolyzing it to the corresponding enone (**58**). This compound (**58**) was then alkylated with allyl iodide to form (**59**) in moderate yield. Compound (**59**) was then subjected to ozonolysis in the presence of Sudan Red 7B,[14] which selectively cleaved the more electron rich double bond to give the 1,4-dicarbonyl compound (**60**) in quantitative yield.

Scheme XVII



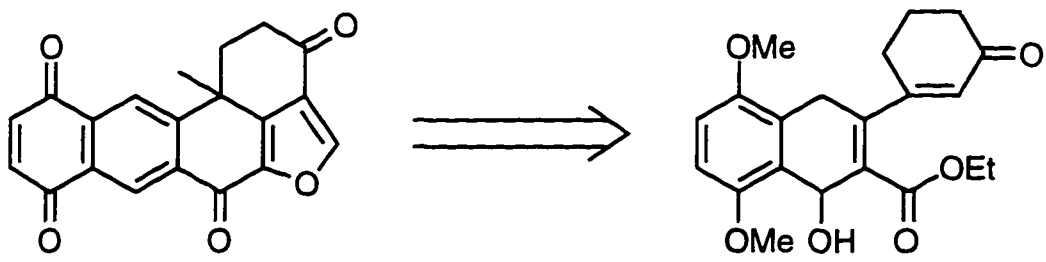
(**51**) (**58**)



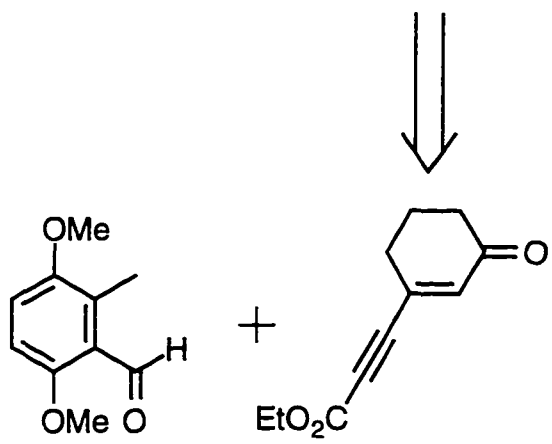
(**59**) (**60**) (**61**)

Unfortunately, all attempts to convert compound (**60**) to the desired furan (**61**) met with failure (Scheme XII). Various mineral acids and Lewis acids were tried without any success. Conversion of the aldehyde on compound (**60**) to its corresponding cyanohydrin and then treating with various acids also failed to give the desired furan (**61**). Due to the lack of success, this approach was quickly abandoned.

Scheme XVIII



(**1**) (**62**)



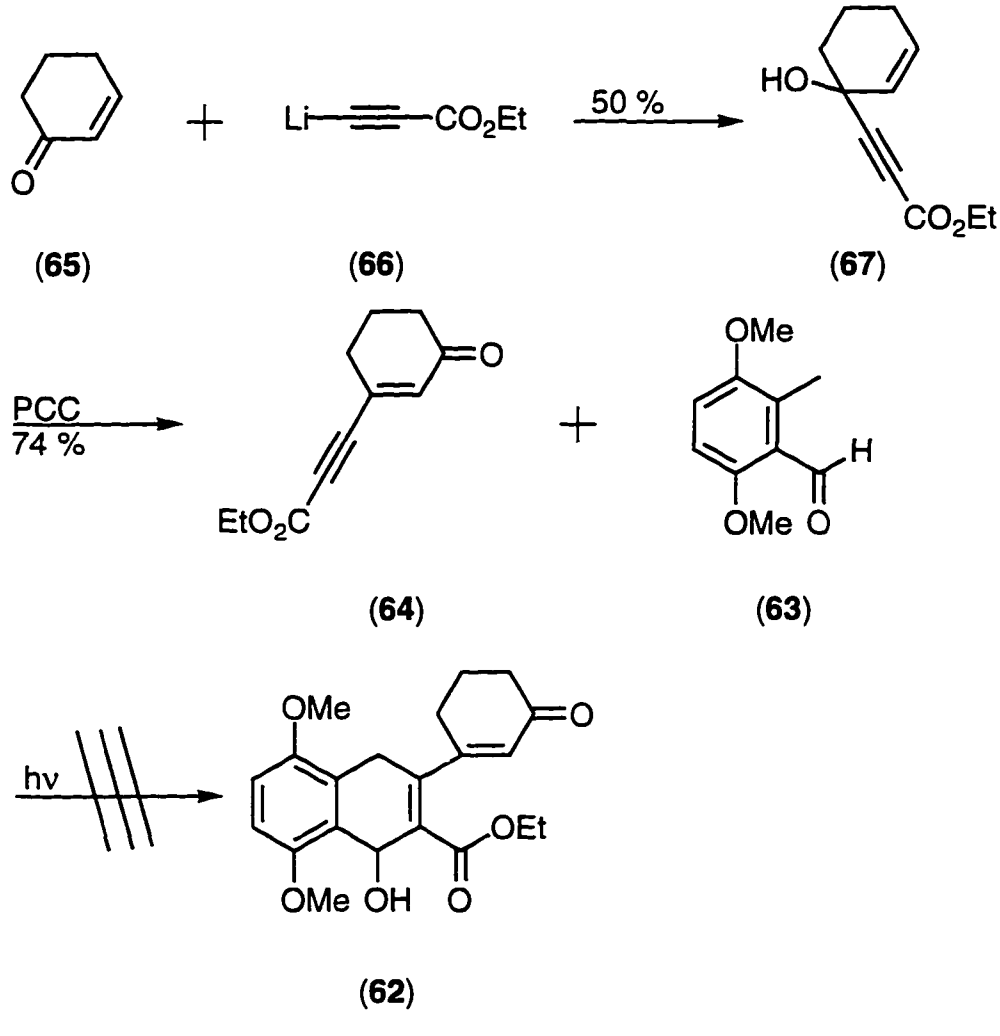
(**63**) (**64**)

We changed our strategy once again. This time we proposed an intermolecular [4+2] cycloaddition as our key step (Scheme XVIII). Photolysis of a mixture of compounds (**63**) and (**64**) would give an intermediate such as compound (**62**). This intermediate (**62**) could be readily dehydrated to form the naphthalene ring, and in addition 1,4-addition of a cuprate to the enone would give

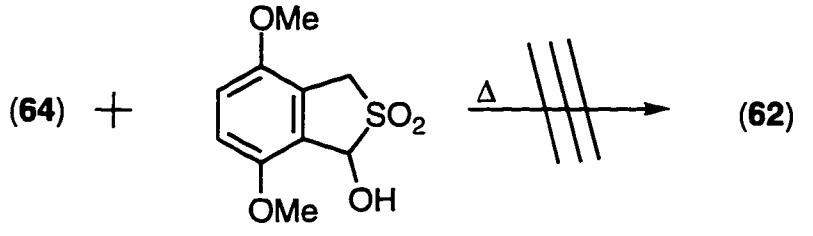
the desired methyl substituent of halenaquinone (**1**). The compound (**62**) also provided handles for installing the last two rings.

Compound (**64**) was quickly assembled from cyclohexanone (**65**) (Scheme XIX). Treatment of cyclohexanone (**65**) with the lithium anion of ethyl propiolate[15] (**66**) provided the allyl alcohol (**67**) in 50 % yield. Oxidation of (**67**) provided the enone (**64**) in 74 % yield. The aldehyde (**63**) was prepared from the readily available 2,5-dimethoxybenzyl alcohol by lithiation, quenching with methyl iodide and then oxidation of the alcohol. Compounds (**63**) and (**64**) were mixed and irradiated, but none of the desired addition product (**62**) was isolated.

Scheme XIX



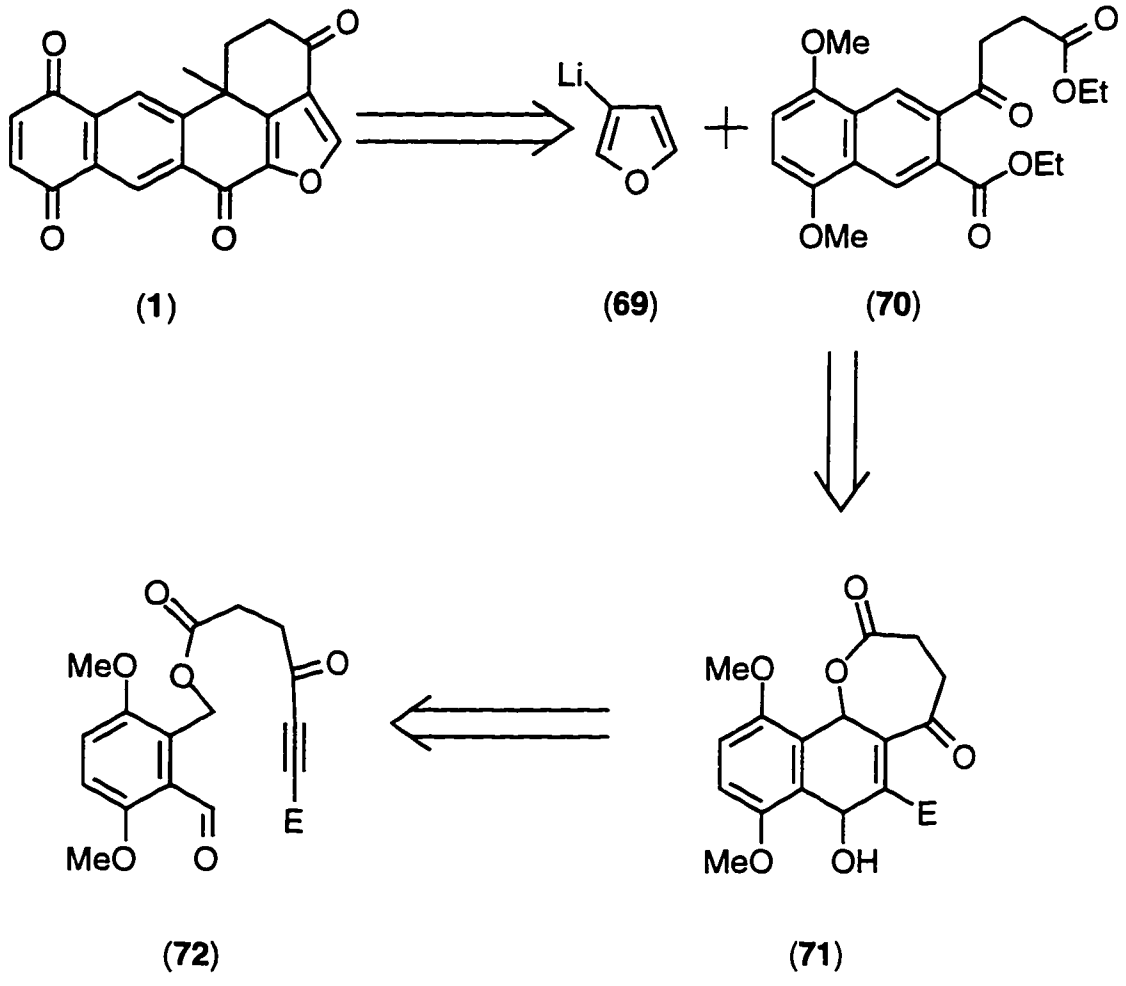
We then tried briefly to cyclize the enone (**64**) with the 1,3-dihydrobenzo[*c*]thiophene 2,2-dioxide[16] (**68**), but once again the reaction met with failure. The reaction eventually worked, but a large excess of the dienophile was required for success. Due to the expense for such a large amount of compound (**64**) and the purification procedures that would be involved, this approach was discontinued.



(**68**)

We then returned to the intramolecular approach and hoped that with a few modifications we would be able to continue. The next idea that we had (Scheme XX) was to add a 3-lithiofuran (**69**) to a compound such as (**70**). We assumed that the nucleophile would add to the benzylic ketone before adding to either of the esters. The resulting compound would still have plenty of functional handles that would be needed for further manipulation to the pentacyclic ring system. We proposed that (**70**) would come from an intermediate such as the tricyclic compound (**71**). The seven-membered lactone (**71**) would be made via our tandem photoenolization/[4+2] cycloaddition sequence from (**72**). This would be an interesting extension of the work that we had already completed. Before we had used this methodology to design 6,6,5-ring systems, and now we were curious if we could apply this same type of strategy to make 6,6,7-ring systems.

Scheme XX

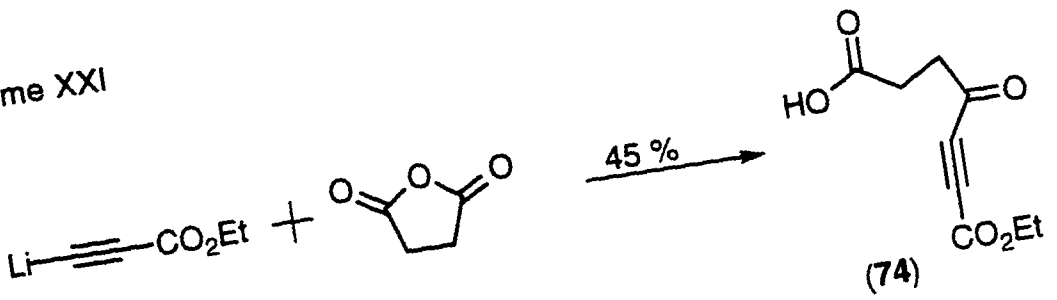


(1) (69) (70)

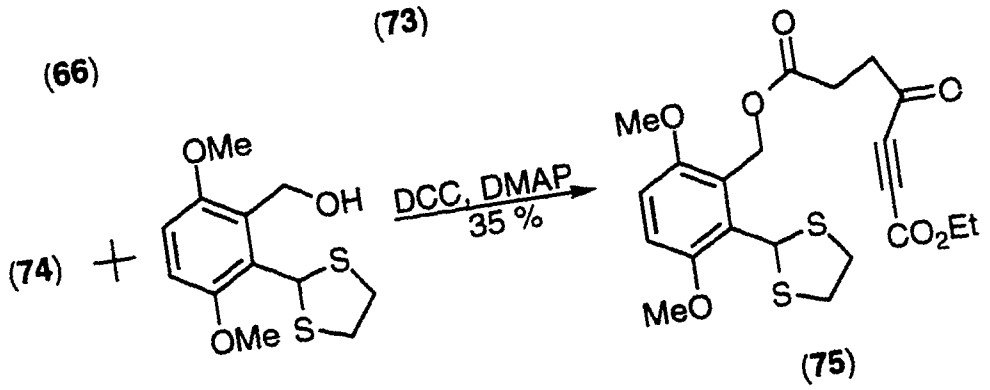
(72) (71)

The first step would be to make the corresponding carboxylic acid that would be used to make the intermediate ester (**72**). Using the lithium anion of ethyl propiolate (**66**),[15] we opened up succinic anhydride (**73**) to form the highly-functionalized carboxylic acid (**74**) in a modest 45 % yield (Scheme XXI). We then coupled this acid (**74**) with the alcohol (**47**) to provide the ester (**75**) in a disappointingly low yield of 35 %. Once again we were not too worried about the low yield, but instead we wanted to focus on the key photoenolization step. Removal of the thioketal protecting group was easily accomplished using the periodane reagent to give the aldehyde (**72**). The aldehyde (**72**) was then subjected to irradiation, and the benzocyclobutenol (**76**) was isolated. This

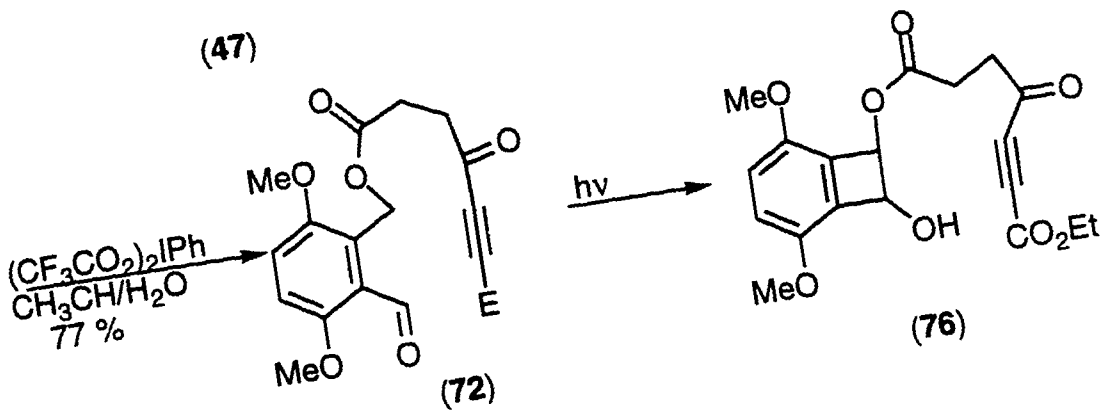
Scheme XXI



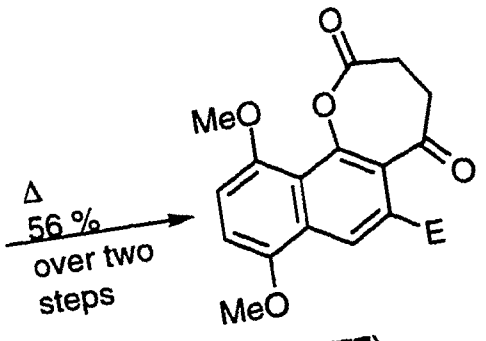
(66) (73) (74)



(47) (75)



(72) (76)



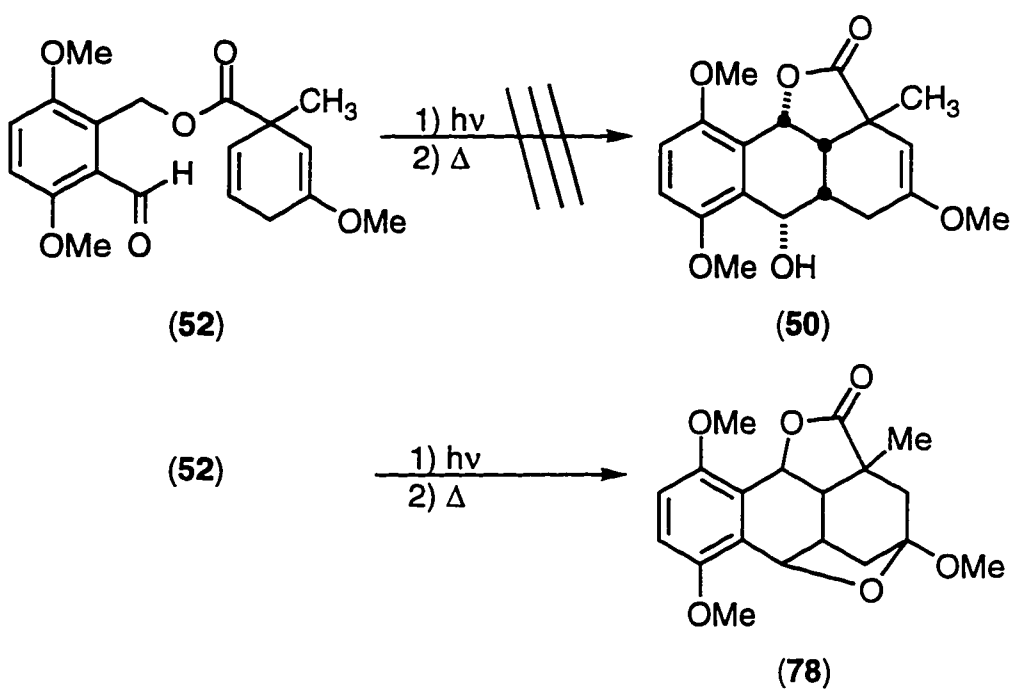
(77)

compound (**76**) was immediately themolyzed to provide compound (**77**) in 56 % yield over the two steps.

It might be mentioned at this point that when doing the tandem photoenolization/[4+2] cycloaddition sequence, one generally obtains a mixture of the desired cycloaddition product and the benzocyclobutenol after the photolysis. In general it is easier to heat this mixture to promote cleavage and cyclization of the benzocyclobutenol to the desired cycloaddition product, rather than isolating both products after the irradiation with light.

We were glad to see that formation of a seven-membered ring was possible using our tandem photoenolization/cycloaddition strategy. However, the product (**77**) had eliminated water and formed a naphthalene ring with our lactone still attached. This presented a problem in that cleavage of the lactone would leave a hydroxyl group on the aryl ring. Elimination of this oxygen and replacement with a hydrogen would be a difficult task, and we felt that it would be best to pursue other avenues.

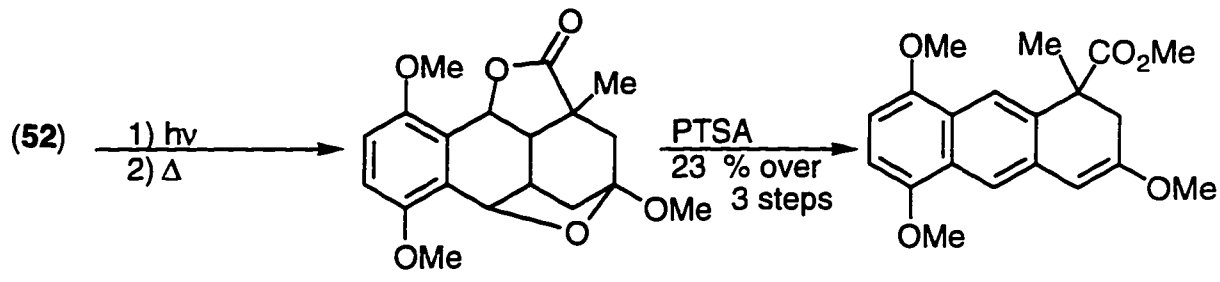
Scheme XXII



At this point, we felt that our best strategy had been the one starting with *m*-anisic acid, doing the Birch reduction, and then alkylating with methyl iodide (Scheme XV). However, we were puzzled as to why the final product (**50**) (Scheme XXII, previous page) from that set of reactions would not undergo elimination of the benzylic alcohol to provide the naphthalene ring. Our original hypothesis was that the tetracyclic ring system was in a conformation such that elimination was not possible. However, upon further examining the question, we came to the conclusion that we had incorrectly identified compound (**50**). Upon further characterization, we concluded that the compound did not have an alcohol present, but instead the alcohol had added to the double bond of the enol ether to form the cyclic ketal. The true structure was in fact compound (**78**).

This would explain why elimination was not occurring when compound (**50**) was treated with methansulfonyl chloride and triethylamine. This structure would also explain the failure of the cyclopropanation reaction (see Scheme XVI) because the carbene had no alkene upon which to react. We also made the observation that we did not try to eliminate the alcohol using *p*-toluenesulfonic acid (PTSA), and that we had only tried to eliminate with basic conditions. Upon examining the structure, we realized that treating compound (**78**) with an acid should cause aromatization of the ring, providing us with a valuable intermediate towards our synthesis of halenaquinone (**1**).

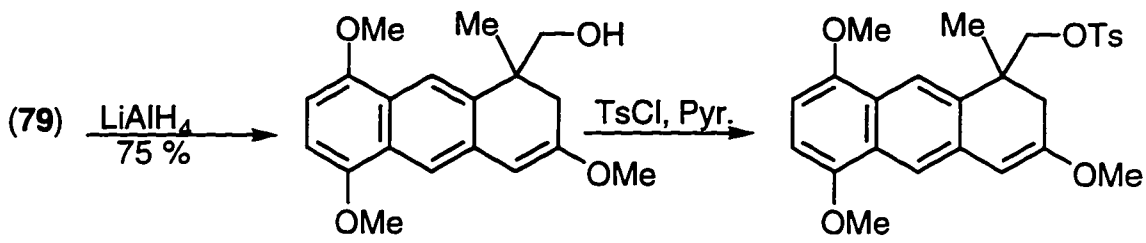
We treated the compound (**78**) with PTSA in refluxing methanol and were pleased to discover that we obtained compound (**79**). Generally, it was easier to do the photolysis, thermolysis, and the elimination all in one sequence without purification. Purification after each step did not increase yields and was rather cumbersome. In addition, subjecting compound (**78**) to the conditions of silica gel chromatography hydrolyzed the cyclic ketal, causing a loss of material as well complicating the purification procedure.



(78) (79)

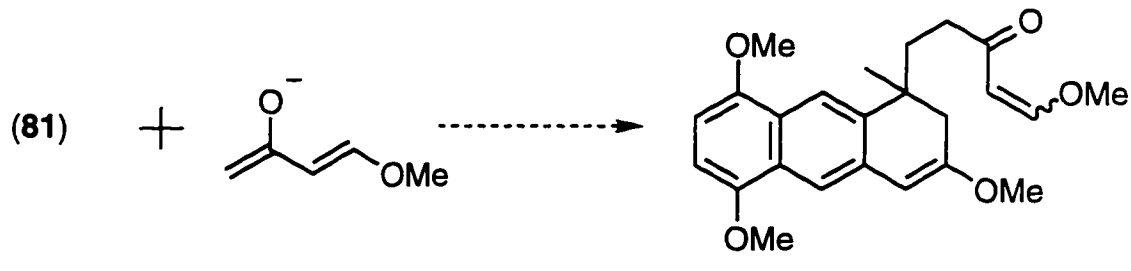
We were somewhat surprised to obtain the methoxy enol ether in compound (**79**) as we expected to get the dimethoxy acetal instead. We attempted to run the reaction under milder conditions, but we were unsuccessful as elimination of methanol occurred too easily. We later attempted to form the dimethoxy acetal by using mercuric acetate in methanol followed by reduction with sodium borohydride,[17] but once again only starting material was recovered as elimination of methanol was too facile.

With compound (**79**) in hand, our first plan of attack was to reduce the ester and convert it to some type of leaving group. We would then attack it with some type of nucleophile and cyclize the final two rings. Therefore, we treated the ester (**79**) with lithium aluminum hydride to provide the alcohol (**80**) in 75 % yield. The alcohol was then converted to the tosylate (**81**).



(80) (81)

The nucleophile that we wanted to add to compound (**81**) was the anion of 4-methoxy-3-buten-one (**82**). The resulting product (**83**) would then contain functionality that could be transformed into the furan ring of halenaquinone (**1**) as well as correctly positioning one of the carbonyls. Unfortunately, we were dismayed to discover that the anion of 4-methoxy-3-buten-2-one does not alkylate well except if the electrophile is an acid chloride.[18] With the leaving group occupying a neopentyl carbon, attack by a nucleophile would be modest at best. Therefore, we decided to change our plans.

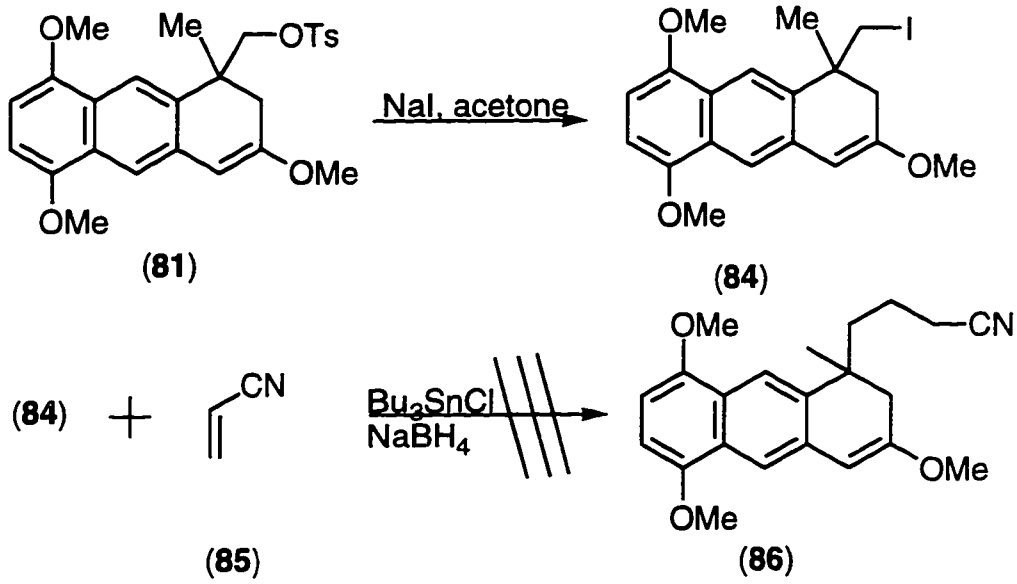


(**82**) (**83**)

We planned to work around the neopentyl carbon issue by resorting to radical chemistry. Radicals are not as susceptible to steric hindrances as are nucleophiles.[19] First compound (**81**) was converted to a radical precursor by changing the tosylate to the corresponding iodide (**84**) (Scheme XXIII). We then attempted to add acrylonitrile (**85**) to compound (**84**) by initiating the radical with tri-*n*-butyltin hydride,[20] but we were unsuccessful in obtaining compound (**86**).

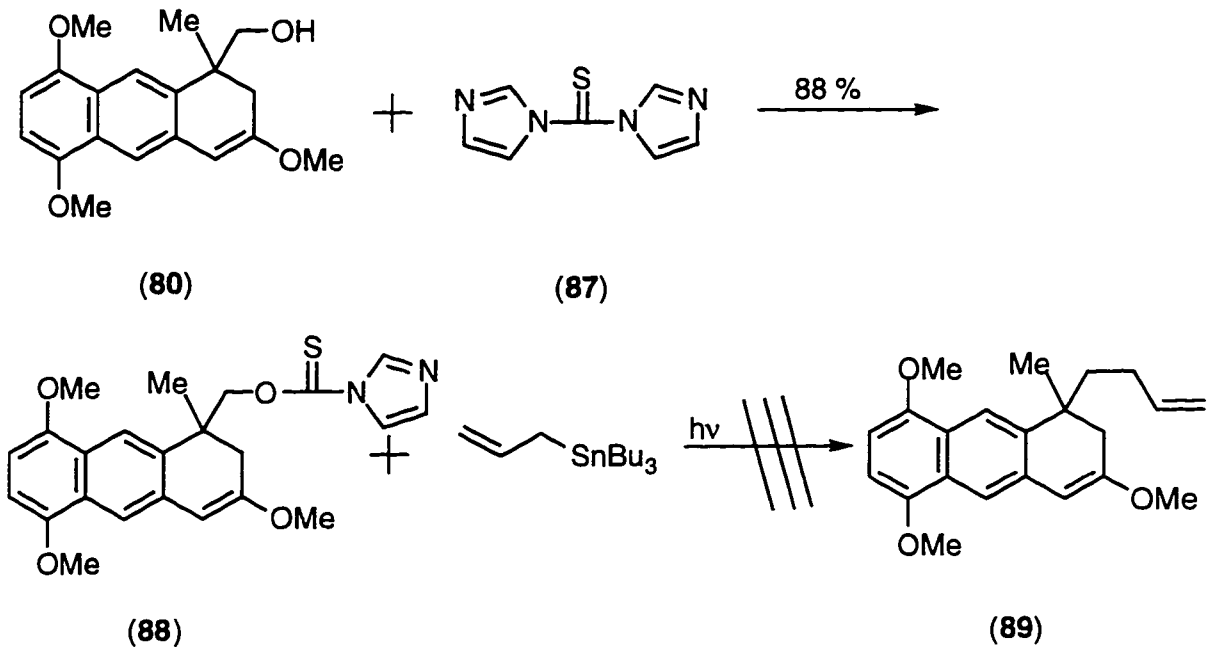
We then tried a different radical source by converting the alcohol (**80**) to the corresponding thioacylimidazole (**88**) (Scheme XXIV). Using the chemistry developed by Keck,[21] we then attempted to add an allyl group to this compound (**88**) by photolyzing a mixture of (**87**) with allyltri-*n*-butylstannane, but once again

Scheme XXIII



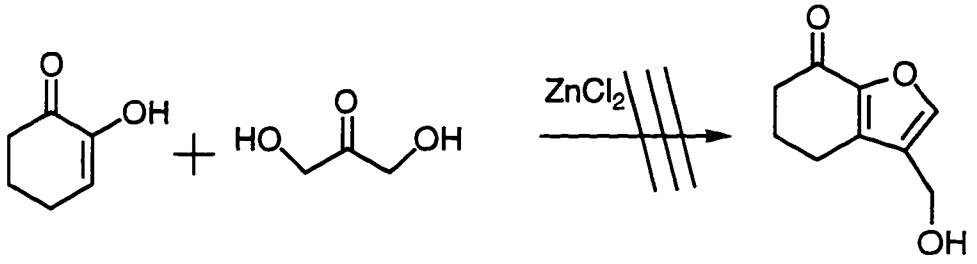
we were unable to isolate the addition product (**89**). Due to the lack of success that we were having with the radical chemistry, both photochemically and thermally, we decided to abandon the idea for the moment and focus our efforts on a different type of reaction.

Scheme XXIV



At this point, we began to run low on the amount of material that we had available so we began to redirect our efforts towards building a model system before trying any more chemistry on the real system. The model system that we chose to build was a cyclohexanone ring fused to a furan in hopes that we could build an analog of halenaquinone (**1**). We started with 1,2-cyclohexanedione because we felt that we could convert any of the compounds that we made (**79** or **80**) into a dione by dihydroxylating the double bond and then oxidizing.

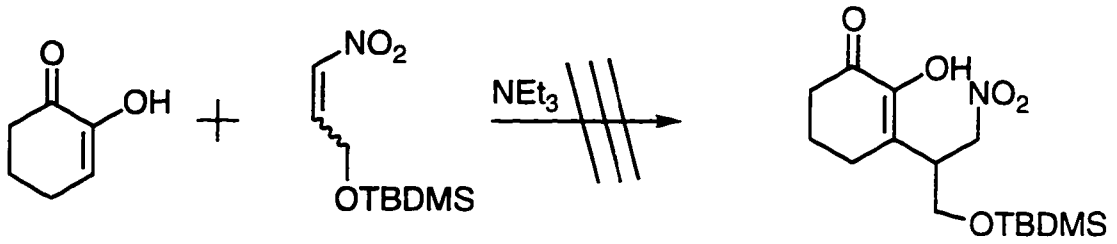
Working in conjunction with the MS-444 project, we tried to assemble the furan ring using chemistry developed by Hanson.[22] We combined 1,2-cyclohexanedione[23] (**90**) with dihydroxyacetone (**91**) and zinc chloride in hopes that we could form the furan (**92**). A system of this sort could be applied to a dione derived from (**79**) to give the corresponding furan which would contain a functional handle for completing the final ring of halenaquinone (**1**). Unfortunately, we were unsuccessful in our efforts to make the furan (**92**).



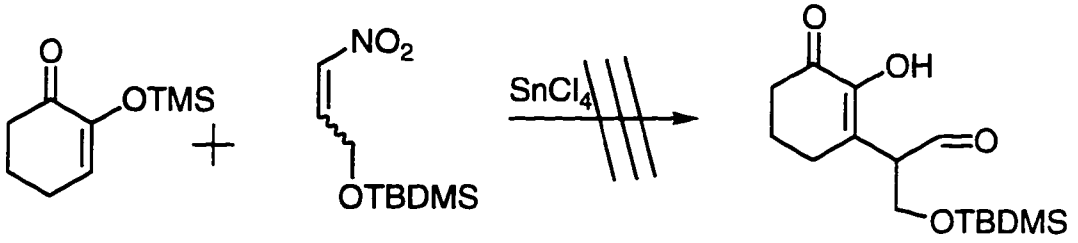
(**90**) (**91**) (**92**)

We then tried to establish the furan system by a Michael addition sequence, using a nitro alkene as the Michael acceptor. Hydrolysis of the nitro group and elimination would then lead to the desired product. However, we were unsuccessful at adding the nitro alkene (**93**) to 1,2-cyclohexanedione (**90**) (Scheme XXV), even after trying a wide variety of conditions. We were also unsuccessful at adding the nitro alkene to the monosilyl ether of 1,2-dicyclohexanedione (**95**), using the procedure developed by Yoshikoshi.[24]

Scheme XXV



(**90**) (**93**) (**94**)



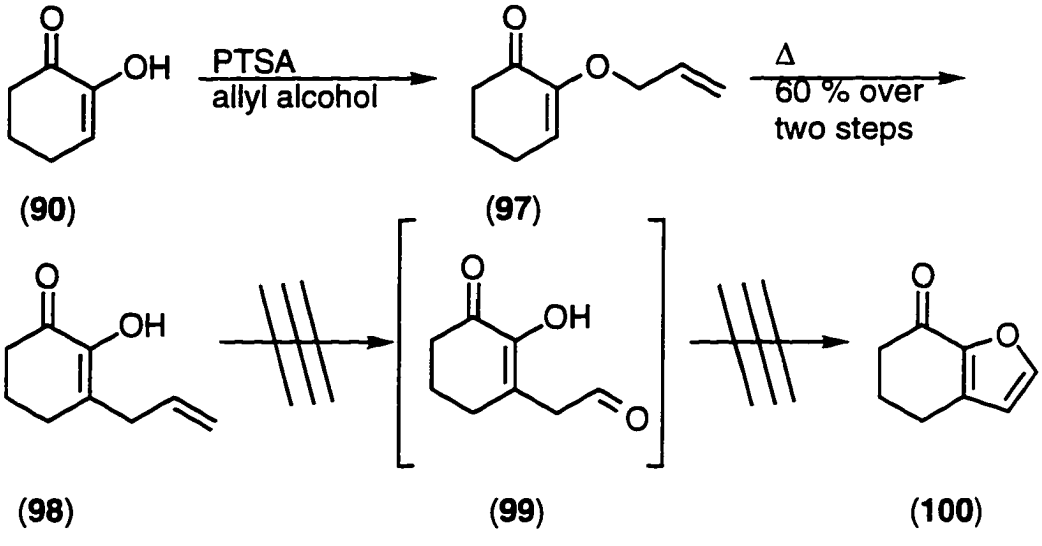
(**95**) (**93**) (**96**)

The final attempt that we made at constructing a model system involved making the monoallyl ether (**97**)[25] and subjecting it to the Claisen rearrangement to provide compound (**98**) in 60 % yield (Scheme XXVI). With this compound (**98**) in hand, we hoped to convert the allyl double bond into an aldehyde by ozonolysis. Selectivity between the two alkenes would hopefully be achieved by using Sudan Red III as an indicator.[14] Unfortunately, the enone alkene was too electron rich, and no selectivity could be obtained, providing nothing but a mixture of products.

Conclusions

We have demonstrated a unique pathway to the core skeleton of halenaquinone (**1**) via a tandem photoenolization/[4+2] cycloaddition sequence. We have obtained a ring structure which contains three of the five rings found in halenaquinone (**1**). In addition, the intermediate that we have made has the potential for further manipulation into the target molecule.

Scheme XXVI



(90) (97)

(98) (99) (100)

Experimental

Unless otherwise noted, materials were obtained from commercial suppliers and used without additional purification. Diethyl ether and tetrahydrofuran (THF) were distilled from sodium benzophenone ketyl. Benzene was distilled from lithium aluminum hydride. Toluene and methanol were distilled from sodium. Dichloromethane (CH_2Cl_2), and acetonitrile were distilled from calcium hydride. All reactions were conducted under an argon atmosphere and all extracts were dried over anhydrous sodium sulfate or anhydrous magnesium sulfate. Apparatus for experiments requiring anhydrous conditions were flame-dried under a stream of argon or dried in a 150 °C oven for 12 hours and cooled under a stream of argon. Alumina chromatography was conducted using activated neutral aluminum oxide, Brockmann I, standard grade (150 mesh), which was purchased from Aldrich Chemical Company. Silica gel chromatography (sgc) was performed on EM Science Kieselgel 60 (mesh 230-400). Thin layer chromatography (tlc) was performed using EM Science Kieselgel F_{254} prepared plates with a thickness of 0.25 mm. The solvent systems were suitable mixtures of hexanes (H) and ethyl acetate (EA) unless otherwise noted. Infrared spectra were obtained on a Perkin-

Elmer 1320 spectrophotometer and are reported in cm^{-1}. Proton nuclear magnetic resonance spectra (300 MHz) were obtained using a Nicolet Magnetics Corporation NMC-1280 spectrometer. All chemical shifts are reported in δ relative to tetramethylsilane as an internal standard. Splitting patterns are designated as s (singlet), d (doublet), t (triplet), q (quartet), dd (doublet of doublets), dt (doublet of triplets), and m (multiplet); the addition of br indicates a broadened pattern. Carbon-13 NMR spectra (75.46 MHz) were obtained on a Nicole NMC-1280 spectrometer and are reported in δ relative to $CDCl_3$ (77.00 ppm) as an internal standard. High resolution mass spectra (HRMS) were obtained on a Kratos model MS-50 spectrometer. Low resolution mass spectra (MS) were obtained on a Finnigan 4023 mass spectrometer. The purity of all title compounds was determined to be > 90 % by ^1H NMR spectral determination.

1,3-Dihydro-1-hydroxy-4,7-dimethoxyisobenzofuran (45). Following the procedure of Chen and Kraus,[10] to a solution of 29.4 g (175 mmol) of 2,5-dimethoxybenzyl alcohol (**44**) in 600 mL of THF was added *n*-BuLi (350 mmol, 140 mL of 2.5M solution) at 0 °C. The resulting solution was boiled for six hours and cooled to 0 °C. *N,N*-Dimethylformamide (15 mL) was then introduced into the solution and the mixture was stirred for 12 hours. After the reaction was quenched with 200 mL of saturated NH_4Cl solution and 1N HCl, the solution was stirred overnight. The white precipitate was collected and the aqueous layer was then extracted with ethyl acetate (200 mL three times). The combined organic layer was washed with brine and dried with $MgSO_4$. The solvent was then concentrated to about 30 mL, and the white solid was collected by filtration to yield 22.7 g (66 %) of a white solid: mp 156-157 °C. ^1H NMR ($CDCl_3$) δ 3.07 (d, J = 7.2 Hz, 1H), 3.80 (s, 3H), 3.84 (s, 3H), 5.00 (d, J = 13.2 Hz, 1H), 5.30 (dd, J_1 = 13.2 Hz, J_2 = 2.1 Hz, 1H), 6.58 (dd, J_1 = 7.2 Hz, J_2 = 2.1 Hz, 1H), 6.74 (d, J =7.4 Hz, 1H), 6.78 (d, J = 7.4 Hz, 1H). IR (film) 3560, 2940, 1500, 1300, 1020 cm^{-1}. TLC (1:1 H:EA) R_f = 0.33.

2-(2-Hydroxymethyl-3,6-dimethoxyphenyl)-1,3-dithiolane (47). Following the procedure of Kraus and Chen,[10] the hemiacetal (**45**) (8.9 g, 45 mmol) was mixed in 150 mL of CH_2Cl_2. To this solution was added 1,2-ethanedithiol (**46**) (5.5 mL, 60 mmol). Boron trifluoride etherate (0.5 mL, 4 mmol) was added to the solution at 0 °C. The resulting mixture was stirred for 12 hours at room temperature. To this mixture, 10 mL of 2N NaOH solution was added, and the solution was stirred for another two hours. The mixture was diluted with 200 mL of CH_2Cl_2 and washed with 50 mL of 2N HCl and brine. The organic layer was then dried over $MgSO_4$. Purification of the crude material was achieved by flash column chromatography over silica gel to give 11.21 g (91 %) of a white solid. ^{1}H NMR ($CDCl_3$) δ 3.05 (t, J = 7.2 Hz, 1H), 3.37 - 3.64 (m, 4H), 3.81 (s, 3H), 3.84 (s, 3H), 5.12 (d, J = 7.2 Hz, 2H), 6.60 (s, 1H), 6.80 (d, J = 9.0 Hz, 1H), 6.86 (d, J = 9.0 Hz, 1H). ^{13}C NMR ($CDCl_3$) δ 40.1, 46.2, 55.3, 55.9, 56.5, 111.1, 111.4, 124.4, 131.1, 151.6, 153.1. TLC (2:1 H:EA) R_f = 0.26.

3-Methoxy-1-methyl-2,5-cyclohexadiene-1-carboxylic acid (51). The following is a slight modification of the procedure of Birch.[13] The *m*-anisic acid (**43**) (10.0 g, 65.7 mmol) was dissolved in 30 mL of THF. To this solution was added 250 mL of ammonia at -78 °C. Pieces of lithium (1.14 g, 165 mmol) were then added cautiously to the slightly heterogeneous reaction mixture until a blue color persisted. Sometimes excess lithium had to be added to maintain the blue color. After 20 minutes, methyl iodide (4.9 mL, 79 mmol) was added slowly to the reaction mixture. The solution was stirred for one hour and quenched with solid NH_4Cl (15 g). The ammonia was allowed to evaporate, and the resulting residue taken up in water. The aqueous layer was extracted once with ether (30 mL). The aqueous layer was then cooled in an ice bath at 0 °C while 3N HCl was added slowly. The temperature of the system must be kept below 5 °C to ensure that isomerization does not occur. Once the solution became acidic, it was extracted with ether (2 X 200 mL). The aqueous layer was re-acidified and extracted again

with ether (2 X 200 mL). The organic layers were combined, washed with brine, and dried over $MgSO_4$. Concentration provided 11.05 g (100 %) of a yellow oil that was generally pure enough for use without further purification. ^1H NMR δ 1.42 (s, 3H), 2.72 (s, 2H), 3.66 (s, 3H), 4.80 (s, 1H), 5.85 (s, 2H).

(2-(1,3-Dithian-2-yl)-3,6-dimethoxyphenyl)methyl 3-methoxy-1-methyl-2,5-cyclohexadiene-1-carboxylate (53). The carboxylic acid (**51**) (4.13 g, 24.6 mmol), the alcohol (**47**) (5.17 g, 18.9 mmol), and 4-dimethylaminopyridine (0.230 g, 1.89 mmol) were dissolved in 80 mL of CH_2Cl_2. To this solution was added a solution of 1,3-dicyclohexylcarbodiimide (5.84 g, 28.3 mmol) in 20 mL of CH_2Cl_2 at 0 °C. The solution was allowed to warm to room temperature overnight and then filtered through a glass frit. The solution was dried over Na_2SO_4 and concentrated. The crude material was then subjected to flash column chromatography over silica gel (6:1 H:EA) to provide 5.33 g (67 %) of a clear viscous oil. ^1H NMR ($CDCl_3$) δ 1.35 (s, 3H), 2.65 - 2.68 (m, 2H), 3.29 - 3.35 (m, 2H), 3.53 - 3.57 (m, 5H), 3.76 (s, 3H), 3.83 (s, 3H), 4.80 (d, J = 1.1 Hz, 1H), 5.44 (s, 2H), 5.69 (dt, J_1 = 10.0 Hz, J_2 = 3.3 Hz, 1H), 5.77 - 5.83 (m, 1H), 6.34 (s, 1H), 6.86 (AB quartet, J_1 = 17.7 Hz, J_2 = 9.1 Hz, 2H). IR (film) 2932, 1732, 1593, 1485, 1098, 732 cm^{-1}. MS (CI) m/z 422, 255, 226, 195, 123. HRMS m/z calculated for $C_{21}H_{26}O_5S_2$: 422.1222, measured 422.1211. ^{13}C NMR ($CDCl_3$) δ 28.6, 40.6 (2C), 46.0, 46.9, 54.1, 56.5, 56.8, 58.3, 97.4, 111.9, 113.2, 122.5, 125.4, 127.5, 129.4, 152.4, 153.3, 153.6, 175.8. TLC (2:1 H:EA) R_f = 0.56.

(2-Formyl-3,6-dimethoxyphenyl)methyl 3-methoxy-1-methyl-2,5-cyclohexadiene-1-carboxylate (52) To a solution of the thioacetal (**53**) (3.6 g, 8.52 mmol) in 16 mL of acetonitrile/water (9:1) was added potassium carbonate (5.89 g, 42.6 mmol). To this heterogeneous solution was added the [bis(trifluoroacetoxy)iodo]benzene (5.5 g, 12.8 mmol) at 0 °C. The solution was stirred for six hours and poured into a sodium bicarbonate solution. The organic

layer was washed with brine, dried over Na_2SO_4, and concentrated. The crude material was then subjected to flash column chromatography (6:1 H:EA to 4:1 H:EA) on silica gel that had been washed with a 3 % triethylamine solution in hexanes. This afforded 1.75 g (59 %) of a white solid: mp 113-115 °C. ^{1}H NMR ($CDCl_3$) δ 1.29 (s, 3H), 2.62 (s, 2H), 3.52 (s, 3H), 3.77 (s, 3H), 3.85 (s, 3H), 4.70 (s, 1H), 5.41 (s, 2H), 5.66 - 5.69 (m, 2H), 6.96 (d, J = 9.2 Hz, 1H), 7.08 (d, J = 9.1 Hz, 1H) 10.52 (s, 1H). IR (film) 2892, 1723, 1684, 1589, 1482, 1268, 1103, 813, 718 cm^{-1}. MS (CI) m/z 347, 225, 179. HRMS m/z calculated for $C_{19}H_{22}O_6$: 346.1416, measured 346.1413. ^{13}C NMR ($CDCl_3$) δ 28.3, 28.4, 45.9, 53.9, 56.2, 56.7, 57.3, 97.1, 112.7, 117.5, 122.5, 124.9, 125.2, 129.1, 152.4, 153.2, 156.3, 175.3, 191.6. TLC (2:1 H:EA) R_f = 0.39.

Methyl 1-methyl-3,5,8-trimethoxy-1,2-dihydroanthracene-1-carboxylate (79). A benzene solution (65 mL) of aldehyde (**52**) (1.05 g, 3.03 mmol) was degassed with argon for 30 minutes and was then photolyzed with a Rayonet reactor for ten hours. The solution was concentrated and dissolved in toluene and heated in a sealed tube at 210 °C for 24 hours. Concentration provided compound (**78**). This compound (**78**) was then generally taken on without further purification.

Compound (78). However, purification over silica gel chromatography (5:1 H:EA to 1:1 H:EA) provided a viscous oil. ^{1}H NMR ($CDCl_3$) δ 1.56 (s, 3H), 1.82 (d, J = 6.2 Hz, 1H), 1.86 (d, J = 4.3 Hz, 1H), 2.31 - 2.38 (m, 1H), 2.47 - 2.52 (m, 1H), 2.77 (dd, J_1 = 13.9 Hz, J_2 = 2.2 Hz, 1H), 3.02 - 3.08 (m, 1H), 3.42 (s, 3H), 3.81 (s, 3H), 3.83 (s, 3H), 5.26 (d, J = 2.5 Hz, 1H), 6.15 (d, J = 10.3 Hz, 1H), 6.86 (s, 2H). IR (film) 2960, 1757, 1488, 1264, 1107. TLC (2:1 H:EA) R_f = 0.15.

The crude mixture of compound (**78**) was then dissolved in 150 mL of MeOH. *p*-Toluenesulfonic acid monohydrate (0.057 g, 0.300 mmol) was then

added, and the solution was heated at reflux overnight. The solution was then diluted with CH_2Cl_2 and washed with saturated sodium bicarbonate solution. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated. The crude material was purified via flash column chromatography (10:1 H:EA) to give 0.235 g (23 % over 3 steps) of a viscous oil. ^{1}H NMR ($CDCl_3$) δ 1.73 (s, 3H), 2.44 (d, J = 16.1 Hz, 1H), 3.09 (d, J = 16.1Hz, 1H), 3.66 (s, 3H), 3.74 (s, 3H), 3.94 (s, 6H), 5.78 (s, 1H), 6.58 (d, J = 8.4 Hz, 1H), 6.64 (d, J = 8.3 Hz, 1H), 7.80 (s, 1H) 8.06 (s, 1H). IR (film) 2951, 1731, 1648, 1462, 1271, 1092, 722 cm^{-1}. MS (CI) m/z 343, 320, 303, 288. HRMS m/z calculated for $C_{20}H_{22}O_5$: 342.1467, measured 342.1472. ^{13}C NMR ($CDCl_3$) δ 24.2, 38.2, 47.8, 52.3, 54.8, 55.4, 55.6, 96.4, 102.1, 103.4, 117.0, 118.4, 124.1, 125.9, 133.0, 133.8, 148.9, 149.5, 158.6, 176.1. TLC (4:1 H:EA) R_f = 0.41.

1-Hydroxymethyl-1-methyl-3,5,8-trimethoxy-1,2-dihydroanthracene (80). To a solution of ester (**79**) (0.030 g, 0.088 mmol) in 3 mL of ether was added lithium aluminum hydride (0.033 g, 0.88 mmol) at 0 °C. The reaction was monitored by TLC. The excess $LiAlH_4$ was carefully quenched with water and then 1N NaOH was added. After stirring for one hour, water was again added, and the solution was filtered and extracted with ether. The organic layers were combined, washed with brine, dried over $MgSO_4$, and concentrated to provide 0.0202 g (75 %) of a white solid that quickly decomposed unless stored at 0 °C under an argon atmosphere. ^{1}H NMR ($CDCl_3$) δ 1.44 (s, 3H), 2.40 (d, J = 16.7 Hz, 1H), 2.55 (d, J = 16.7 Hz, 1H), 3.56 (d, J = 11.0 Hz, 1H), 3.72 - 3.76 (m, 4H), 3.94 (s, 6H), 5.75 (s, 1H), 6.58 (d, J = 8.3 Hz, 1H), 6.64 (d, J = 8.3 Hz, 1H), 7.78 (s, 1H) 8.03 (s, 1H). ^{13}C NMR ($CDCl_3$) δ 23.4, 36.8, 41.2, 54.7, 55.5, 55.7, 68.5, 96.4, 102.1, 103.3, 117.4, 117.6, 124.1, 125.8, 133.7, 135.6, 148.9, 149.4, 158.6. TLC (4:1 H:EA) R_f = 0.18.

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GENERAL CONCLUSIONS

It is the duty of the synthetic chemist to incorporate all disciplines of organic chemistry into his or her intellectual arsenal. The task of building complex natural products demands that he or she use all of his or her skills to finish the project quickly and efficiently. In addition to these intellectual skills, the synthetic chemist must also be innovative and willing to try new ideas to solve the various problems which he or she may encounter.

In conclusion, we have developed pathways to a number of different natural products and several of their biologically interesting analogs. In the first project, we developed a pathway that completed four of the five rings of eburnamonine. This same pathway was then used to complete a variety of indolo[2,3-*a*]quinolizine analogs, proving its generality and versatility. In the second project, we developed a pathway to the core structure of MS-444, a biologically interesting compound. We also developed methodology that can be used for synthesizing highly-functionalized furans. Finally, in the third project, we have developed a synthetic pathway to the core structure of halenaquinone. The intermediates that we have synthesized have functional handles which enable further manipulation to the target molecule. Hopefully, one day this goal may be realized.

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