1990

Synthesis of polycyclic natural products

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Order Number 9110564

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Iowa State University, 1990

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Synthesis of polycyclic natural products

by

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A Dissertation Submitted to the
Graduate Faculty in Partial Fulfillment of the
Requirements for the Degree of
DOCTOR OF PHILOSOPHY

Department: Chemistry
Major: Organic Chemistry

Approved:

Signature was redacted for privacy.

In Charge of Major Work

Signature was redacted for privacy.

For the Major Department

Signature was redacted for privacy.

For the Graduate College

Iowa State University
Ames, Iowa
1990

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DEDICATION

To my parents, wife and children

GENERAL INTRODUCTION

Organic synthesis remains a dynamic and central area of organic chemistry. There are many new principles, strategies and methods of synthesis waiting to be discovered. It is the widespread belief that a key aspect of synthetic design is efficiency — the ability to transform readily available starting materials into target compounds via the shortest possible routes.

This thesis will deal with a new synthetic approach to pyranonaphthoquinone antibiotics and diterpene alkaloids.

Explanation of Thesis Format

This thesis is written so that each part represents an article in a publishable form. The numbering scheme adopted for the compounds and references is independent in each section.

PART I.

NEW SYNTHETIC APPROACH TO PYRANONAPHTHOQUINONE ANTIBIOTICS

INTRODUCTION

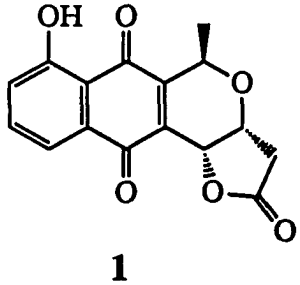
The useful biological activity and unique structure of pyranoquinones have prompted considerable synthetic attention. It is clear from an examination of their structures that the primary difference lies in the substitution pattern on the naphthoquinone subunit. Our interest in developing a common intermediate for all of these natural products led us to plan a new synthetic approach.

This manuscript will detail our three step (Michael addition, oxidation and reduction) sequence for pyranolactone subunits and Michael addition/aldol condensation methodology for the production of C-glycosyl compounds.

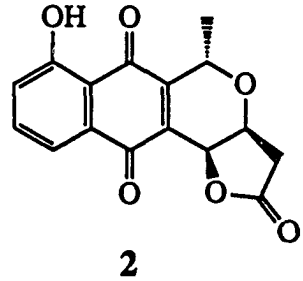
HISTORICAL

Quinones constitute an important class of compounds that show wide-ranging biological activities.[1,2] Many naphthoquinone-derived natural products show significant antibiotic and antitumor properties.[3,4] Among them, the pyranonaphthoquinone antibiotics are a growing class of compounds which were isolated from various species of Stretomyces. Its important members include the nanaomycins (NNM), frenolicins, medermycins, granaticins, SCH-38519, and the arizonins.

The nanaomycin (NNM) group is the largest group in the pyranonaphtho-quinone antibiotics. Kalafungin (**1**), the enantiomer of nanaomycin D (**2**), was isolated in 1968 by workers at the Upjohn company from Streptomyces tranashiensis strain kala (UC-5063).[5,6] The absolute configuration of kalafungin was determined by single crystal X-ray analysis.[7]

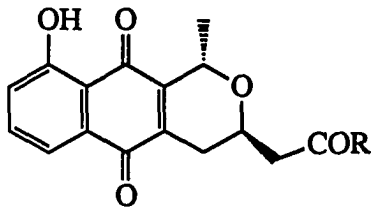


1

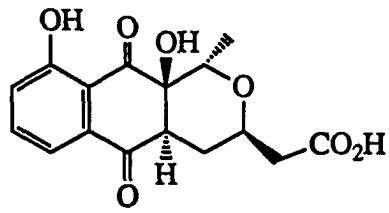


2

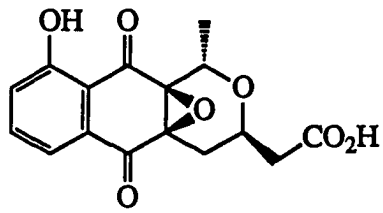
Nanaomycin A (**3**), nanaomycin B (**4**), nanaomycin C (**5**), nanaomycin D (**2**) and nanaomycin E (**6**) were produced from S. rosa subsp. notoensis, which were named after the place where the soil sample was collected.[8,9]



3 R = OH
5 R = NH_2



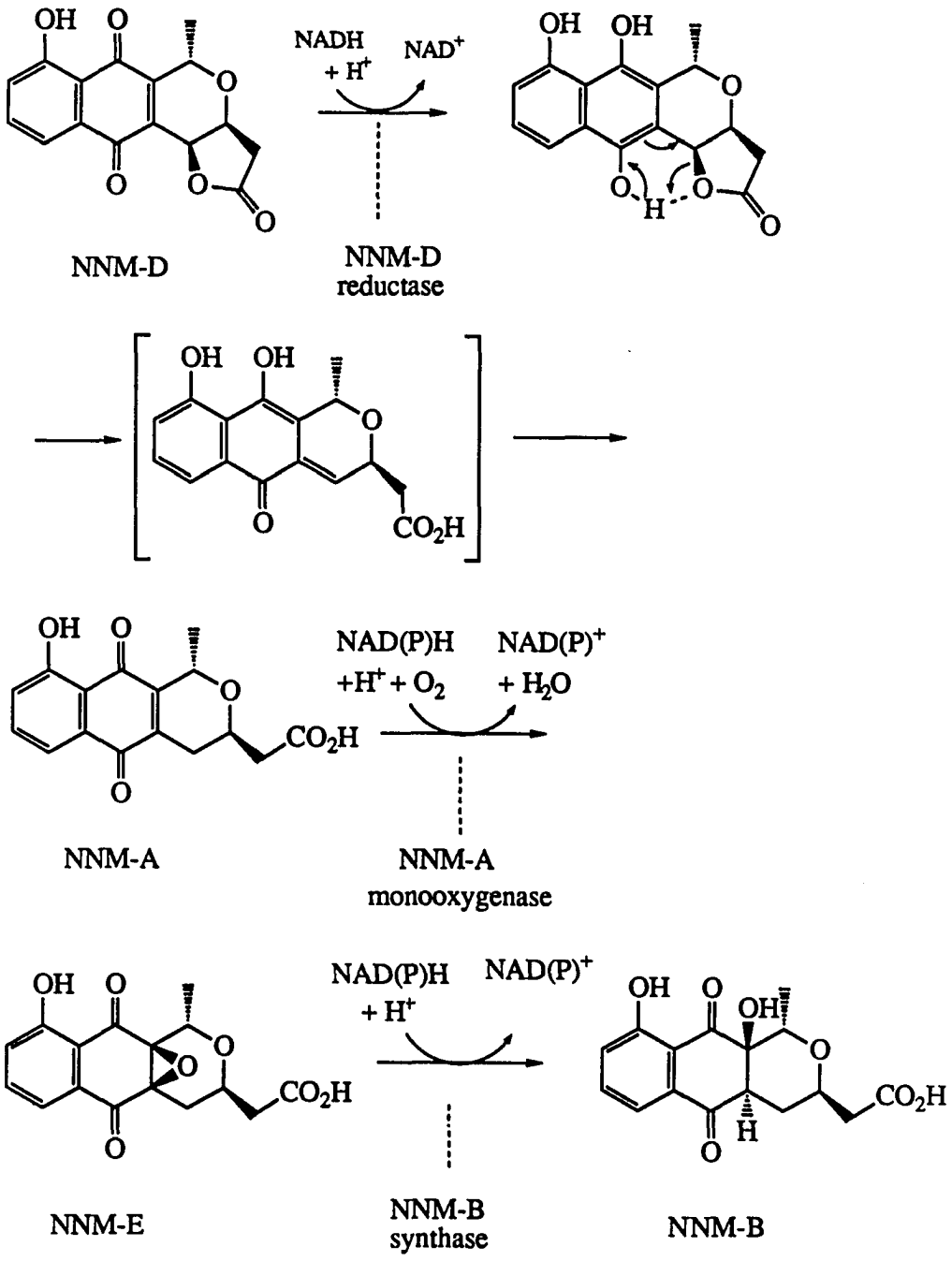
4



6

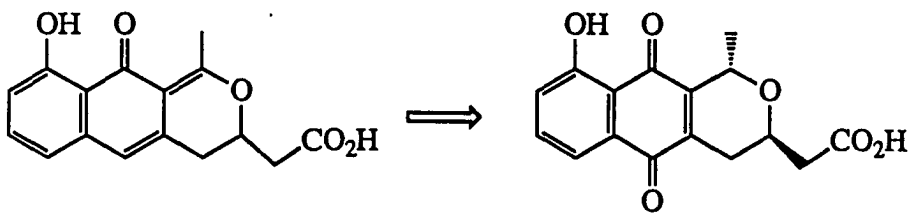
Nanaomycin shows moderate antibacterial activity and strong activity against mycoplasma, as well as activity against Trichophyton Spp. in vitro. Hamana et al.[10] studied the complex dermatomycosis of cattle. With a single application of 100 ppm of nanaomycin A, the dermatomycosis caused by Trichophyton Verrucosum was healed in one month. After safety tests were conducted, it was approved as an antifungal antibiotic for veterinary use.

The probable biosynthetic pathway for nanaomycin was elucidated through the use of a radiolabeled acetate.[11] The detailed biosynthesis of each component of the nanaomycin complex was studied by use of a cell-free system from S. rosa. Subsp. Notoensis.[12] Three kinds of enzymes involved in nanaomycin biosynthesis were characterized.


NADH
+ H+
NAD+
NNM-D
NNM-D
reductase
NAD(P)H
+H+ + O2
NAD(P)+
+ H2O
NNM-A
NNM-A
monooxygenase
NAD(P)H
+ H+
NAD(P)+
NNM-E
NNM-B
synthase
NNM-B

Among them, nanaomycin D reductase, a flavoenzyme, was purified to homogeneity. Nanaomycin B synthase is the first enzyme known to convert an epoxide group to a monoalcohol.

Recently "yellow pigment" was isolated as an intermediate of biosynthesis of isochromanequinone antibiotics.[13] Yellow pigment was synthesized and biomimetically converted to (±) nanaomycin A.[14]

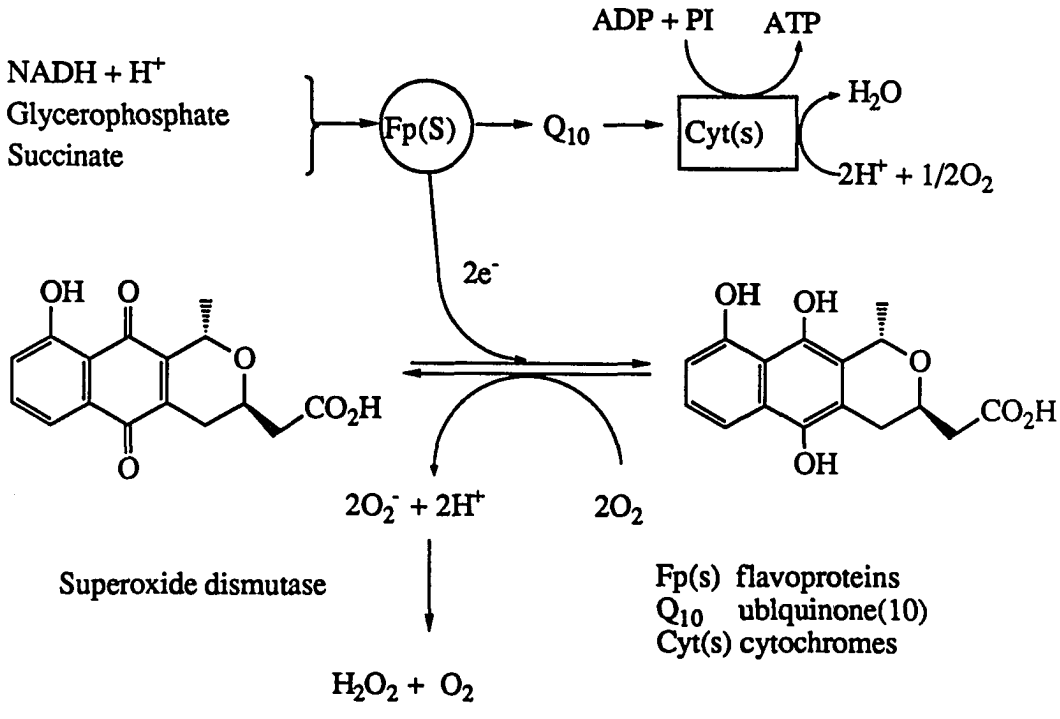


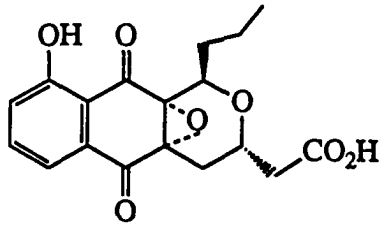
Yellow pigment Nanaomycin A

Hayashi et al. proposed the mechanism of action of these antibiotics in a marine bacterium, Vibrio Alginolyticus.[15]

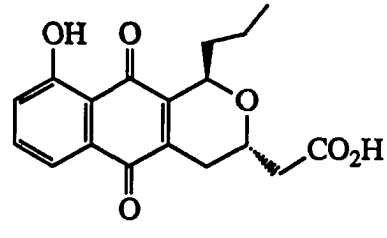
Nanaomycin A receives electrons from respiratory flavoprotein to give a reduced form. When reduced nanaomycin A is oxidized to nanaomycin A by molecular oxygen, superoxide radical (O_3^-) is produced. Superoxide dismutase present in the bacterium acts as a scavenger of O_2^-, but the bacterium is killed due to insufficient digestion and toxicity of O_2^- in the presence of a significant amount of nanaomycin A.

The frenolicins are another subclass of pyranonaphthoquinone antibiotics. Frenolicin **7**,[16,17] deoxyfrenolicin **8**, [17,18] and frenolicin B (**9**)[18] have been isolated and their structures determined as C-1 n-propyl analogs of the nanaomycins.

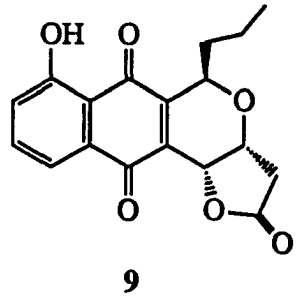

ADP + PI
ATP
NADH + H+
Glycerophosphate
Succinate
Fp(S)
Q10
Cyt(s)
H2O
2H+ + 1/2O2
2e-
OH
O
CO2H
2O2- + 2H+
2O2
Superoxide dismutase
H2O2 + O2
Fp(s) flavoproteins
Q10 ublquinone(10)
Cyt(s) cytochromes


OH
O
CO2H

7


OH
O
CO2H

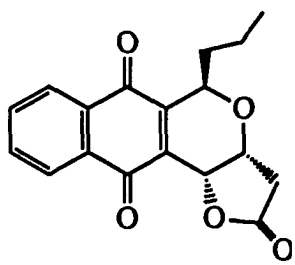
8


OH
O

9

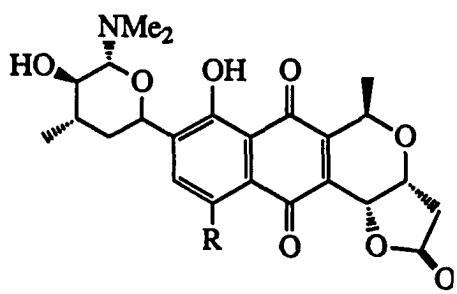
The frenolicin subclass is also active against bacteria, pathogenic fungic and mycoplasmas. Frenolicin B is particularly effective against Eimeria tenella, a pathogen of concern to the poultry industry.[19]

The biological activities of 9-deoxyfrenolicin B (**10**) are very interesting.[20]



10

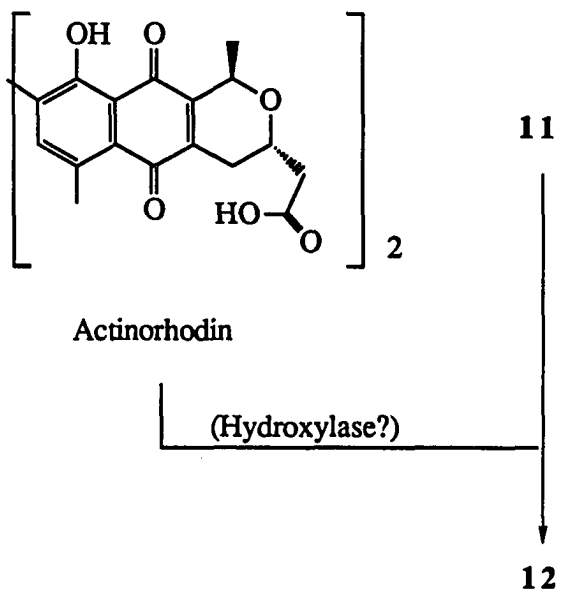
Medermycin (**11**)[21] and mederrhodin A (**12**)[22] are pyranonaphthoquinone antibiotics isolated in 1983 and 1985, respectively. These compounds are similar to the frenolicins in absolute configuration and exhibit low acute toxicity in mice and appear promising as antitumor agents.



11 R = H
12 R = OH

Recently, Hopwood et al. found mederrhodin A. A gene for the enzyme from S. coelicolor which hydroxylates the C-6 of an actinorrhodin precursor was taken and ligated to plasmid vecto PIJ922 and transformed into the medermycin

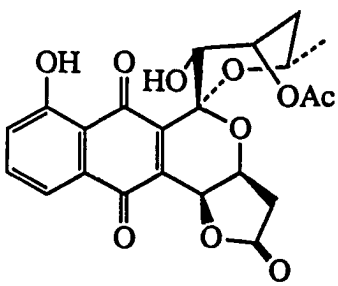
producing strain Streptomyces sp. strain AM-7161. One of the transformants, with plasmid PIJ2315 carrying the gene for the hydroxylating enzyme, produced a new hydroxylated medermycin named mederrhodin. Mederrhodin is the first antibiotic obtained by recombinant DNA technology thus far.



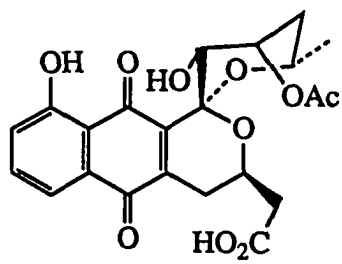
Griseusins A (**13**), griseusins B (**14**), granaticin (**15**) and granaticin B (**16**) are more complex members of the pyranonaphthoquinone family.

Griseusins A and B were isolated from Streptomyces griseusis strain K-63 by Tsuji et al. in 1975.[23]

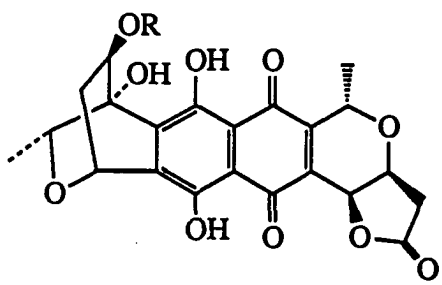
Granaticin was first isolated in 1957 from the culture of Streptomyces oliuceus.[24] It is highly active against gram-positive bacteria and protozoa and exhibits some activity against p-388 cymphocytic leukemia in mice (T/C166% at 1.5 mg/kg) and cytotoxicity against KB cells (ED_{50} 1.6 ug/ml).[25,26] Granaticin B



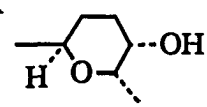
13



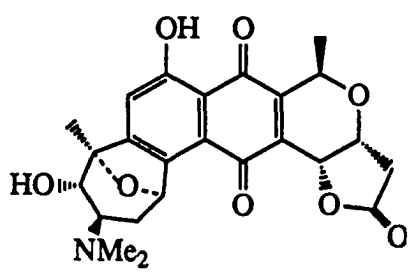
14



15 R = H
16 R =



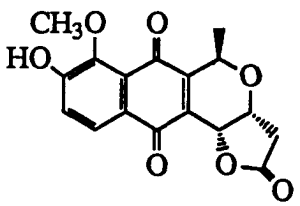
shows a distinct inhibition of various transplanted tumors in rodents after intreperitoneal application. Granaticin has been reported to inhibit RNA synthesis in bacteria by the failure to charge leucyl-tRNA.[27] The cytotoxicity of **15** is attributed to inhibition of ribosomal RNA maturation.[28]



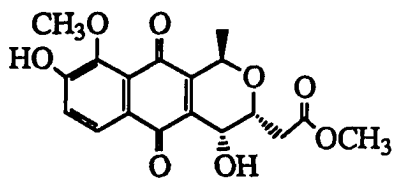
17

SCH-38519 (**17**) is a novel C-glycoside isolated in 1985 .[22,29] It inhibits

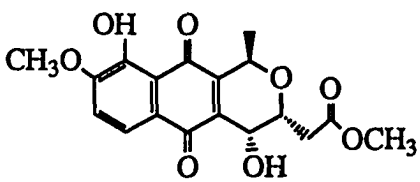
the growth of gram-positive and gram-negative microorganisms. The structure was based on NMR spectral data in combination with an X-ray crystal structure analysis of its hydrochloride salt. This aryl C-glycosyl compound has the phenol group meta to the C-glycosyl linkage unlike medermycin (**11**) which has the phenol group in the ortho position.



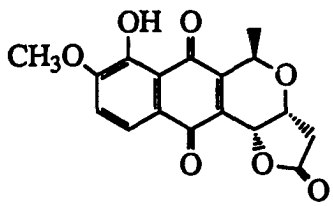
Arizonin A1
18



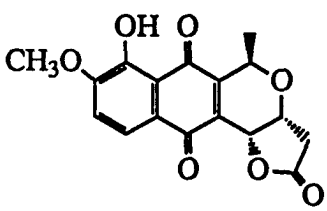
Arizonin A2
19



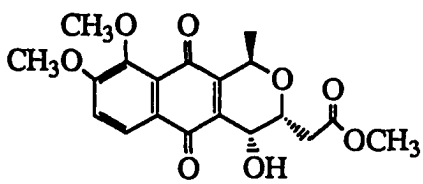
Arizonin B2
21



Arizonin B1
20



Arizonin C1
22

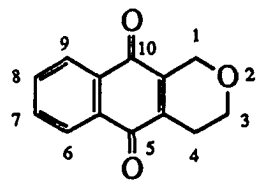


Arizonin C3
23

The arizonins are a new complex of anti-gram-positive antibiotics which was produced by the fermentation of Actinoplanes arizanaensis Sp. nov. The

antibiotics were recovered from the fermentation broth with Amberlite XAD-7 resin and from the mycelium by acetone lysis. UV, IR, MS and NMR spectral studies characterized these compounds as kalafungin-type antibiotics.[30]

Pyranonaphthoquinones show characteristic biological activities and have in common the isochromanquinone skeleton **30**. All contain the 2,3-fused pyranonaphthoquinone ring system in addition to alkyl and acetic acid residues.



10

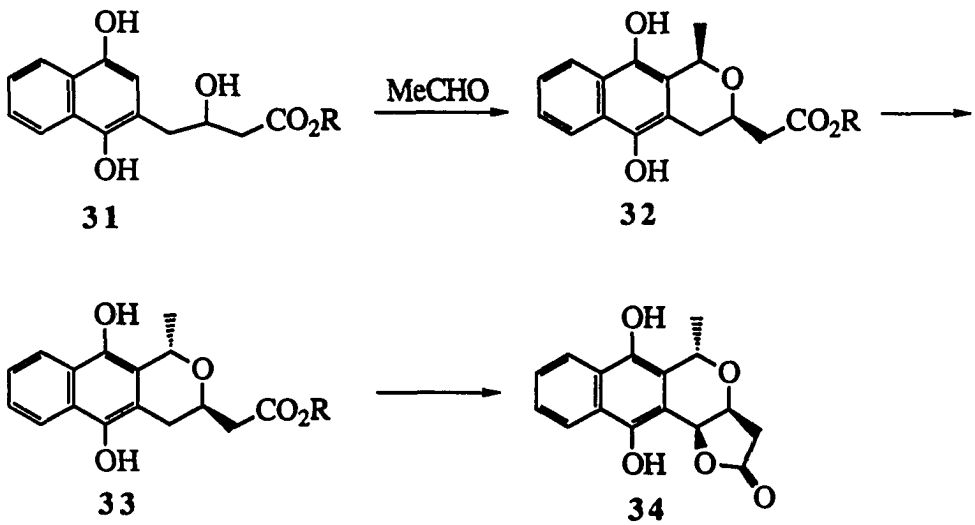
This basic structural type can lead to reactive alkylating agents by in vivo reduction, a process suggested to be responsible for the biological activity of the series. Their interesting biological activity is responsible for the many syntheses.

Due to their useful biological activity, the pyranonaphthoquinones have received considerable attention and have become attractive synthetic objectives. To date, many synthetic routes to these pyranonaphthoquinones have been reported. The successful total syntheses of nanaomycin D, nanaomycin A, kalafungin, frenolicin, deoxyfrenolicin and the enantiomer of griseusin have involved a variety of interesting strategies. These strategies can be divided as follows:

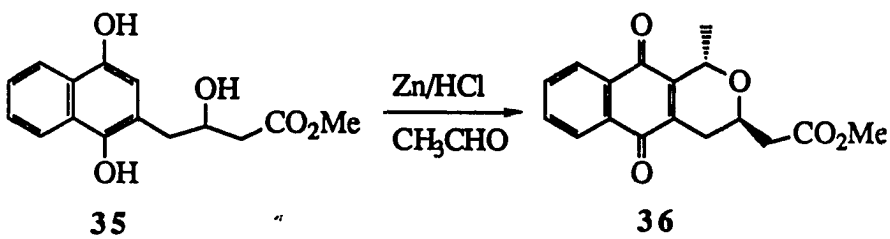
I. Reductive alkylation of naphthoquinones

This strategy originates from Schemie's method[31] for the synthesis of eleutherin and isoeleutherin.[32] The key step involved condensation of the

hydroxyester **31** with acetaldehyde giving the isochroman **32**, which could be converted into the lactone **34** by air oxidation.

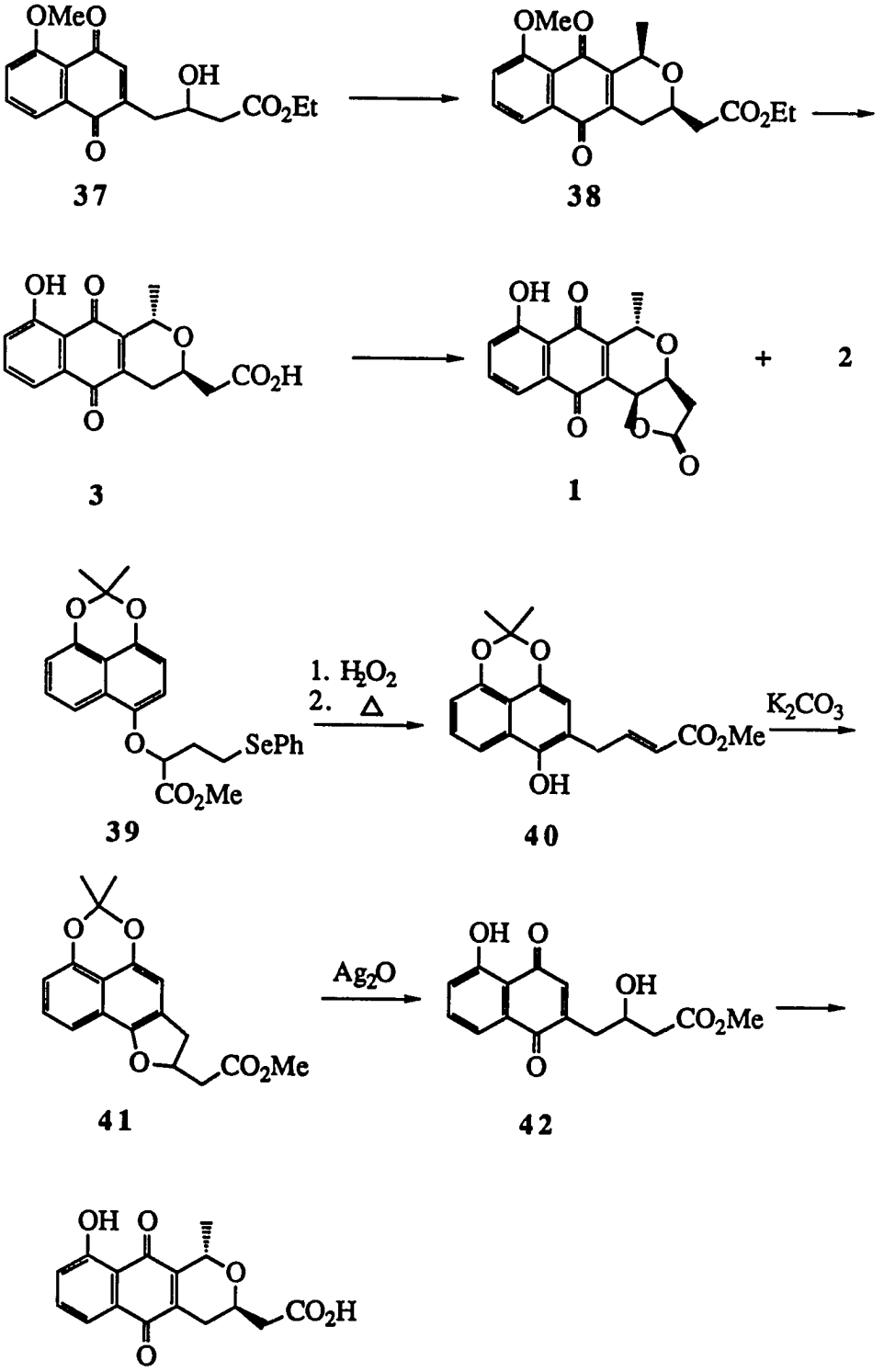


St. Pyrek et al. were the first to utilize this strategy in their synthesis of deoxynanaomycin methyl ester.[33]



The first synthesis of the natural pyranonaphthoquinone antibiotic nanaomycin A was achieved by Li and Ellison.[34]

Compound **37**, which was prepared by a multistep sequence, underwent acetaldehyde addition followed bytreatment with silver(I) oxide to give the cis-pyran **38**. The cis-pyran **38** was converted to nanaomycin A by methyl cleavage,

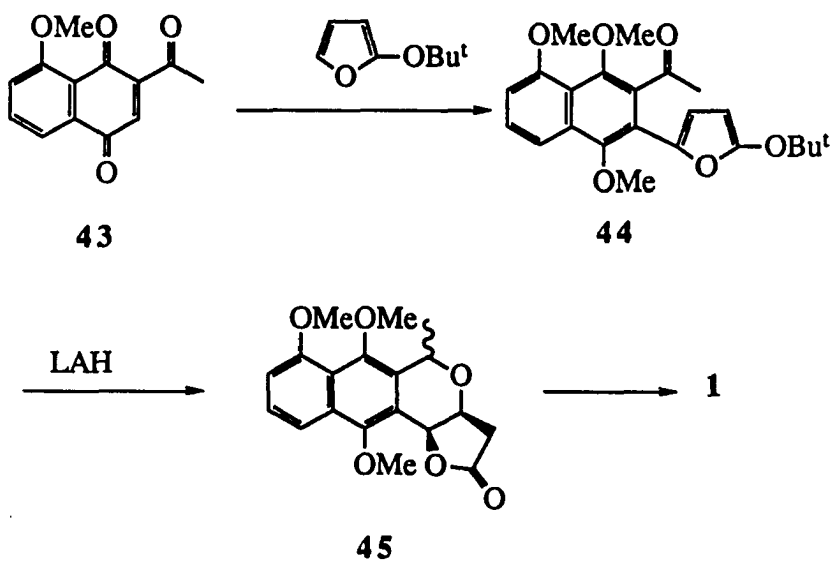

OMeO
OH
CO2Et
O
37
OMeO
O
CO2Et
38
OH O
O
CO2H
3
OH O
O
O
O
1
+ 2
O
O
SePh
CO2Me
39
1. H2O2
2. Δ
O
O
CO2Me
OH
40
K2CO3
Ag2O
OH O
OH
CO2Me
41
42
OH O
O
CO2H

acid catalyzed isomerization and ester hydrolysis. Nanaomycin A with air in methanol gave a racemic mixture of kalafungin and nanaomycin D.

The same strategy was employed by Kometani et al. in 1983.[35] Oxidation of **39**, followed by elimination and Claisen rearrangement produced **40**. Treatment of **40** with base and oxidative cleavage of naphthofuran **41** afforded **42**, which was transformed into nanaomycin A by reactions similar to those in the Li and Ellison synthesis.

II. Addition of nucleophiles to activated naphthoquinones.

The Michael addition of a butenolide equivalent, 2-t-butoxyfuran, with acetylnaphthoquinone **43** gave the condensation product **44**, which was then reductively cyclised to give **45**. This strategy was discovered in 1979 in this laboratory and led to a synthesis of kalafungin.[36]

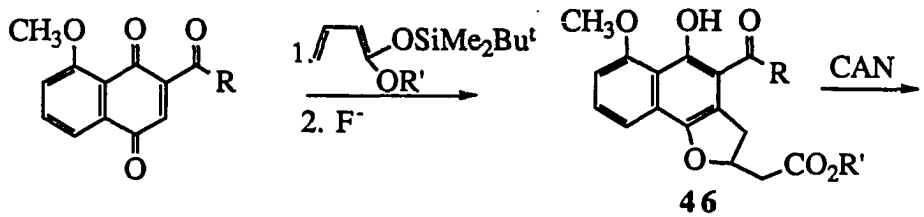


43 **44**

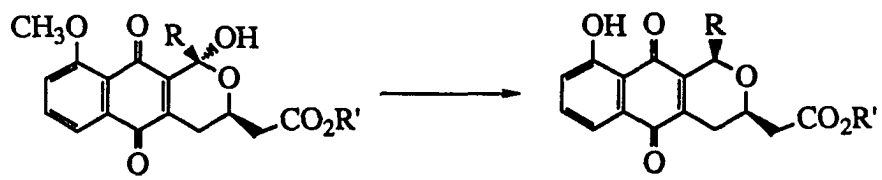
45

This strategy was further developed. Addition of nucleophiles to naphthoquinone followed by tandem Diels-Alder/retro-Claisen (DARC) reaction

produced the carbon skeleton. A stereoselective reduction of a hemiketal made this the most direct and practical synthetic route.[37]



46

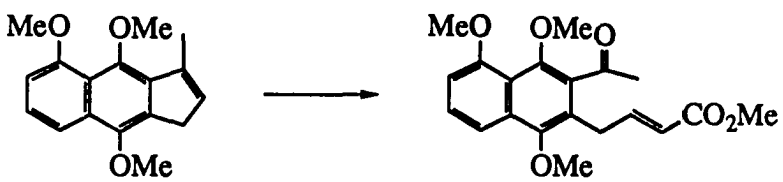


47 R = CH_3, Pr

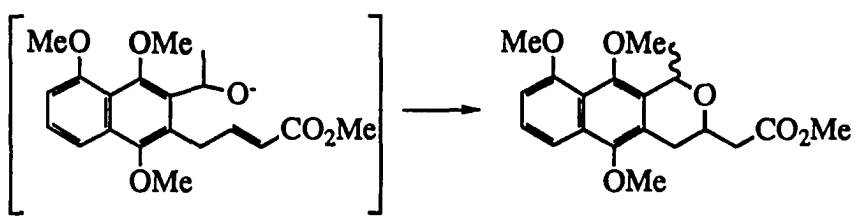
III. Intramolecular alkoxide Michael addition

The construction of the pyran moiety of pyranonaphthoquinones via intramolecular alkoxide Michael addition is another important strategy.

Nanaomycin A has been synthesized using this strategy.[38]



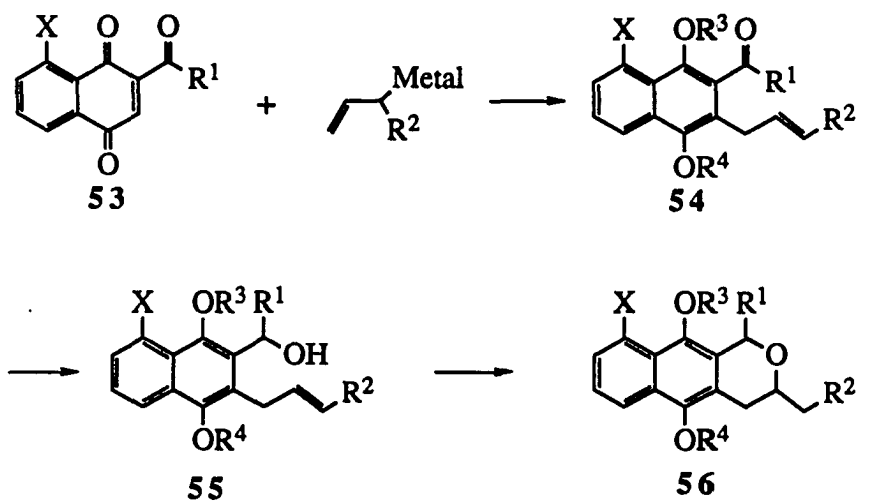
50 51



52

Benzindene **50** underwent oxidation and Wittig olefination to yield **51**. Reduction of **51** with sodium borohydride generated an alkoxide which underwent conjugate addition to give **52**. Ichihara et al. has reported a synthesis of frenolicin by a similar route.[39] The same strategy also was used to build the complex carbon framework of (+)-griseusin A.[40]

The intramolecular alkoxide Michael addition strategy combined with addition of a nucleophile to an activated naphthoquinone is a facile method. Naruta and coworkers have reported a total synthesis of the pyranonaphthoquinone antibiotics eleutherin, isoeleutherin, nanaomycin A and deoxyfrenolicin using this approach.[41]

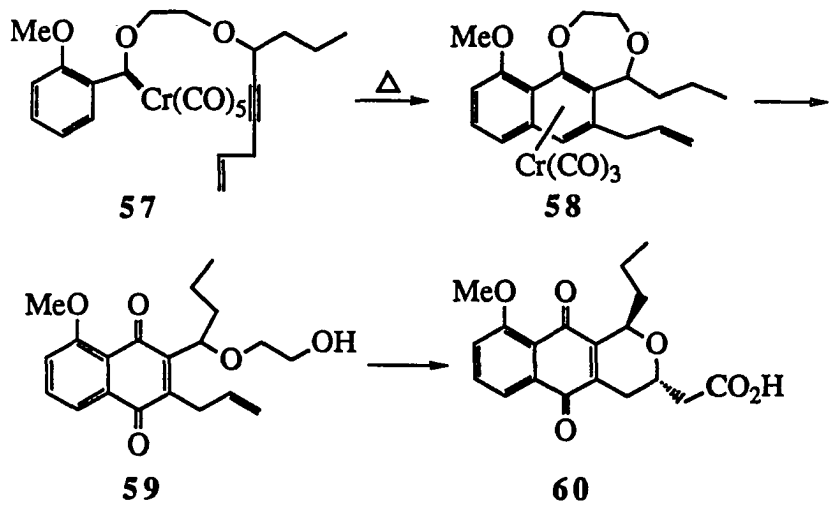


The crucial step in the route is a regioselective allylation of an alkoxy quinone with allylsilanes or allylstannanes. The allylated products are easily converted to pyranonaphthoquinones by intramolecular Michael addition.

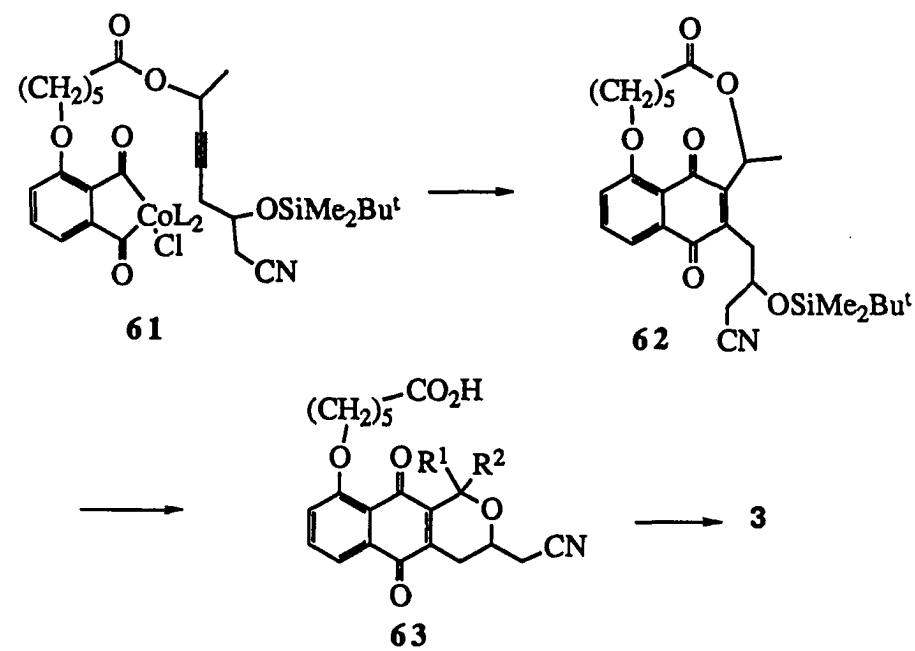
IV. The strategy involving organometallic intermediates

Using an intramolecular chromium-carbene cycloaddition followed by an

intramolecular alkoxide Michael addition, Semmelhack et al. reported the synthesis of deoxyfrenolicin.[42]

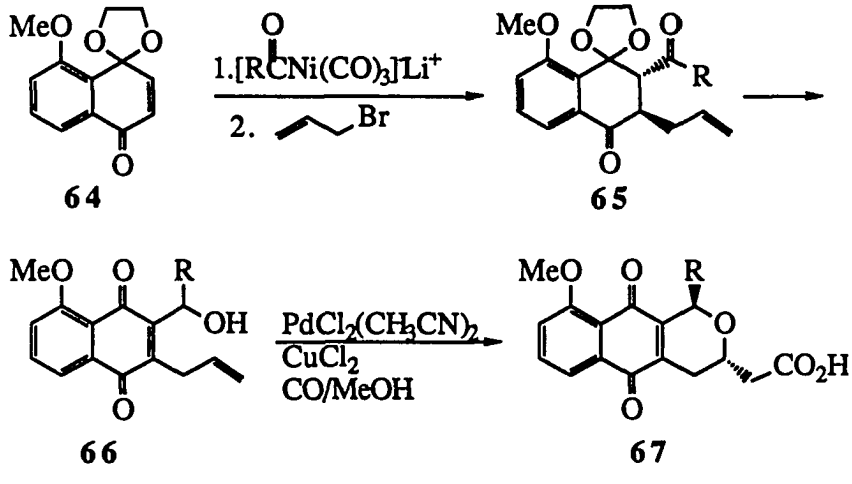


South and Liebeskind reported the regiospecific total synthesis of (±)-nanaomycin A using a phthaloylcobalt complex.[43]



A highly functionalized benzocyclobutenedione substituted with a pendant alkyne was converted in high yield to a phthaloylcobalt complex which underwent regiospecific intramolecular reaction to give macrocyclic naphthoquinone **62**. Conversion of **62** to nanaomycin A was accomplished in three steps involving reductive pyran formation and hydrolysis of a nitrile.

Another synthesis of pyranonaphthoquinone antibiotics involving organometallic intermediates was reported by Semmelhack et al.[44] The nickel complex underwent conjugate addition to the juglone monoketal derivative **64.** Enolate trapping provided **65** in high yield. Hydrolysis to the hydroquinone followed by reaction of the hydroxyquinone under alkoxycarbonylation conditions provided pyrans **67** which were converted to nanaomycin A and deoxyfrenolicin.



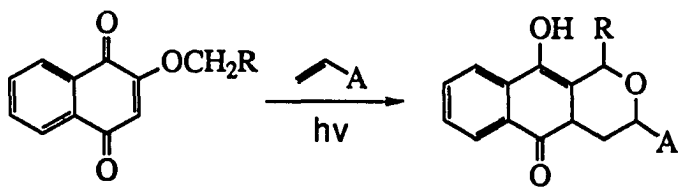
64 65 66 67

The useful biological activity and unique structure of pyranoquinones have prompted considerable synthetic attention. Many elegant syntheses of pyranonaphthoquinone antibiotics have been achieved; however, multistep

sequences for construction of substituted naphthoquinones limit the synthetic utility of many routes.

RESULTS AND DISCUSSION

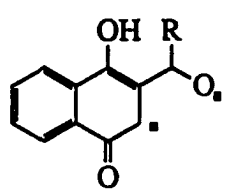
As a result of the sophisticated detection and isolation procedures developed by Omura[45] and others, the family of biologically active pyranoquinones continues to grow rapidly. In development of new synthetic approaches to these compounds, we were intrigued by the novel photochemical reaction show below which had been reported by Otsuki in 1974.[46]



70 **71**

R = H, alkyl, CH_2=CH_2
A = alkyl, Ph

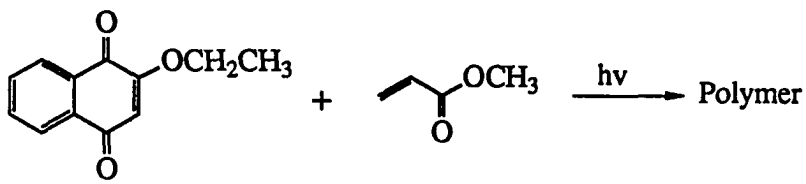
We expected that irradiation of 2-ethoxynaphthoquinone **70** in the presence of unsaturated acids might result in a very direct synthetic route to pyranonaphthoquinones. There were, however, several unanswered questions regarding the stereochemistry of adducts **71**, the generality of the photochemical reaction and the mechanistic pathway of this unusual reaction. The proposed



72

biradical intermediate **72** would probably not afford the regiochemical outcome which was observed.

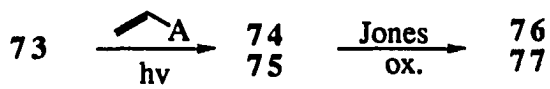
Initially, the reaction of **73** with methyl acrylate was examined. This reaction produced mainly polymers with none of the desired ester.



73

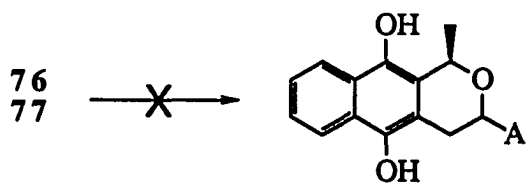
The analogous reaction with 3-buten-1-ol, however, produced adduct **74** in 53% yield after chromatography. This adduct appeared to be a single stereoisomer, as evidenced by proton NMR and CMR spectral analysis. The reaction of **73** with allyl alcohol provided alcohol **75** as a single isomer in 50% yield.

Jones oxidation of **74** and **75** gave acids **76** and **77** in 80% and 85% yield, respectively. Acids **76** or **77** should be a natural precursor to pyranonaphthy-hydroquinones which, in turn, could readily be converted into the pyranonaphthoquinones if the reaction gave products similar to the one reported by Otsuki.[46] However, acids **76** and **77** were recovered after treatment under acidic conditions such as PTSA in THF, concentrated HCl in THF, or mild bases such as triethylamine in acetonitrile.

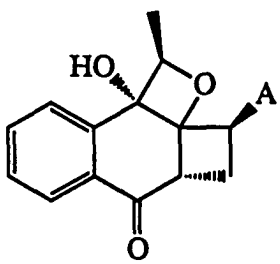


A = CH_2CH_2OH, CH_2OH

The stability of **76** and **77** to acid and mild base seems unusual, particularly since Diels-Alder adducts of benzoquinone can readily be aromatized under similar conditions.[36] This strange result and the unclear regiochemical analysis which was reported by Otsuki prompted us to doubt the photochemical result. Although ^1H NMR spectrum and the exact mass of **74** and **75** supported the structure which had been assigned, the CMR spectra of **74** and **75** indicated



that structure assignment for these compounds was questionable. Fortunately, compound **75** is a highly crystalline solid. X-ray crystallography of compound **75** gave the structure show below (see Appendix). Because of the similarities between the NMR spectra of **74** and **75**, the structure of **74** can also be assigned.

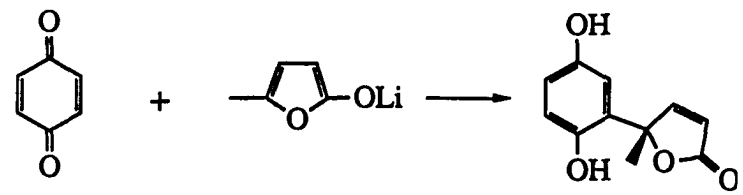


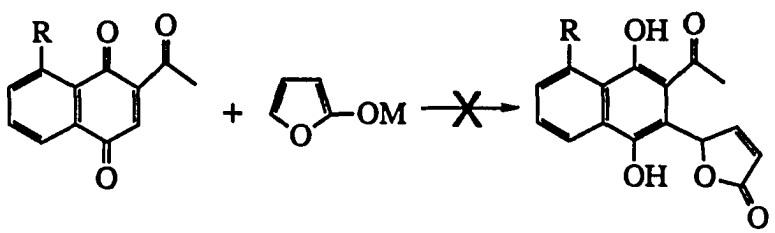
	A
74	CH_2CH_2OH
75	CH_2OH
76	CH_2CO_2H
77	CO_2H

Since the photochemical reaction gave the adducts **74** and **75**, it is not difficult to understand why acids **76** and **77** did not undergo aromatization.

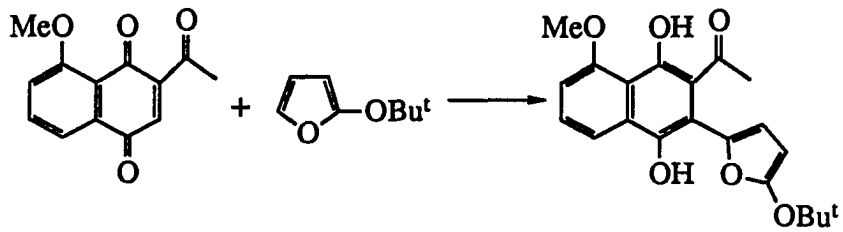
The mechanism by which **74** and **75** are formed probably involves a [2+2] cycloaddition followed by a type II photocyclization. The [2+2] cycloaddition reaction has ample precedent in the photochemistry of quinones.[47] The formation of a highly strained spirocyclic ring system by a type II photocyclization has much less precedent.[48] It is probable that the compounds produced by Otsuki have the spiro structure of **74** and **75**.

With this interesting but disappointing result, we began to seek a new synthetic approach to pyranonaphthoquinones.Previous work from our laboratory demonstrated the facile conjugate addition of butenolide anions to unsaturated carbonyl compounds.[49] Addition of butenolide anions to activated naphthoquinones, however, failed to give similar results.

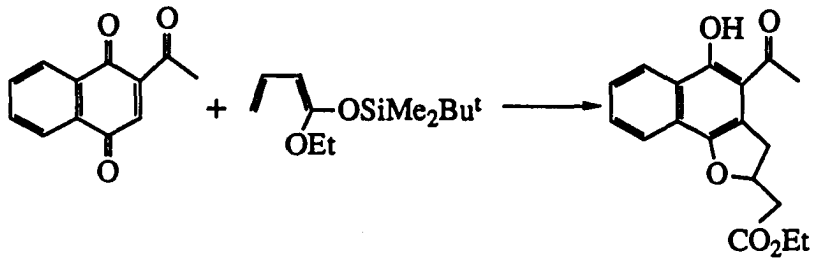




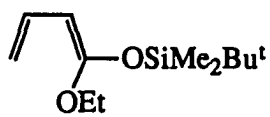
Addition of 2-t-butoxyfuran to activated naphthoquinones gave the Michael addition products.[36]



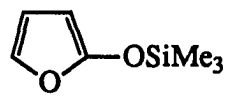
The reaction of acetylnaphthoquinone with 1-ethoxy-1-t-butyl-dimethylsilyloxy-butadiene **84** gave cyclization product which was also observed by Naruta et al.[41] in their studies toward the pyranonaphthoquinones.



Based on this "undesirable" cyclization, it is clear that the substituents on the diene will effect the products of the reaction. The generality of the DARC sequence, plus the similarity of **84** to 2-(trimethylsilyloxy)furan **85** suggests that **85** and activated quinones should undergo a similar reaction.



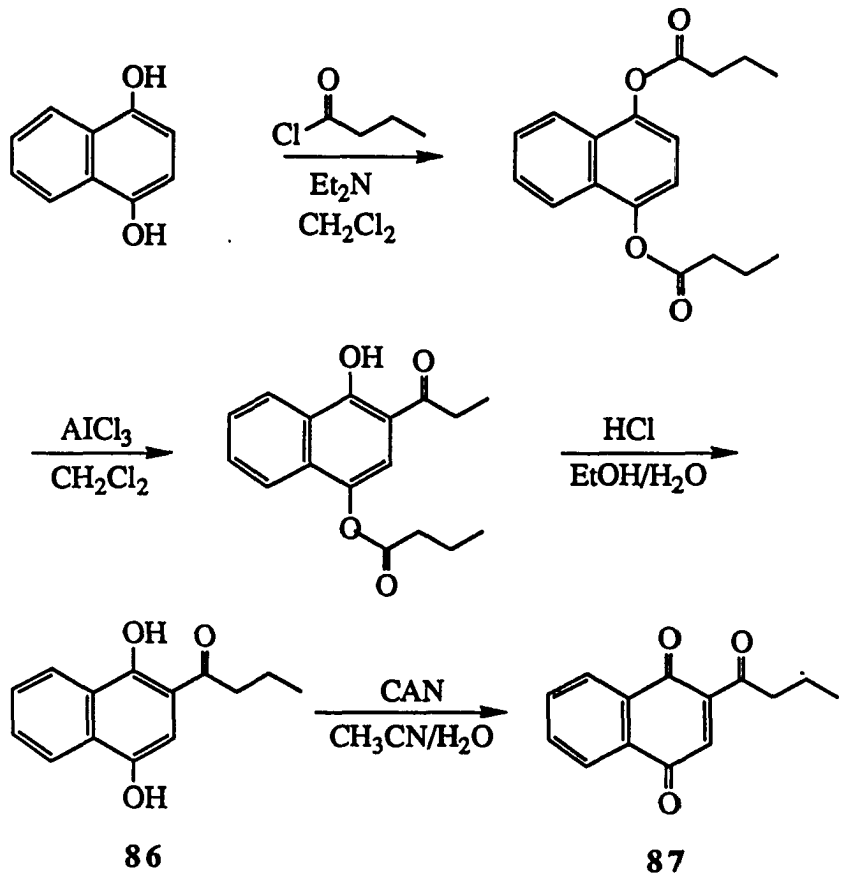
84



85

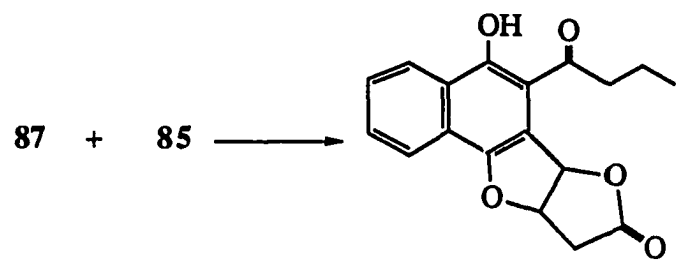
2-Butyrylnaphthyhydroquinone **86** was prepared from naphthyhydroquinone via a three step sequence. It was further oxided with ceric

ammonium nitrate (CAN) in acetonitrile and water to give the 2-butyrylnaphtho-quinone **87**.



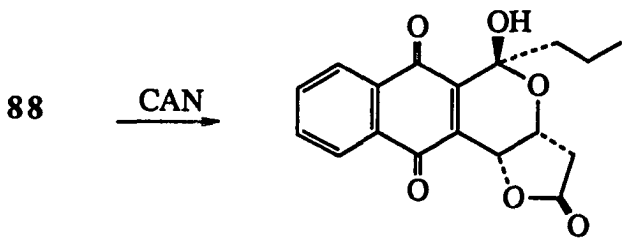
86 **87**

Naphthoquinone **87** is somewhat unstable and in practice it was used

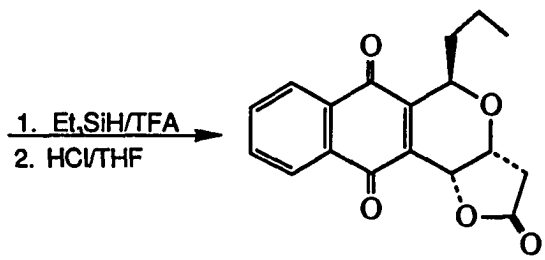


88

without additional purification to react with 2-trimethylsilyloxyfuran **85** to give the cyclization product **88**. Oxidation of **88** with ceric ammonium nitrate gave naphthoquinone **89** which was treated with triethylsilane and boron trifluoride etherate at -78°C to give 9-deoxyfrenolicin B (**10**).



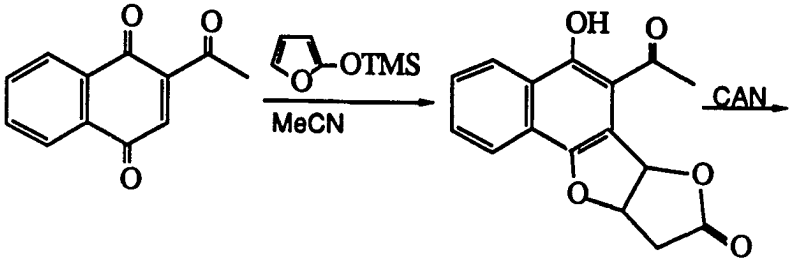
89



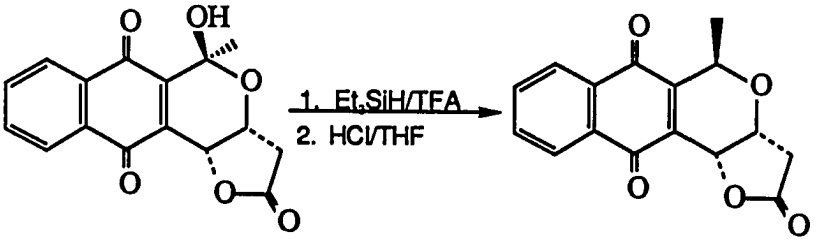
10

To test the generality of this direct route to pyranonaphthoquinone antibiotics, different activated naphthoquiones were used. 2-Acetylnaphthoquinone **90** gave 9-deoxykalafungin **93** via the same three step sequence.

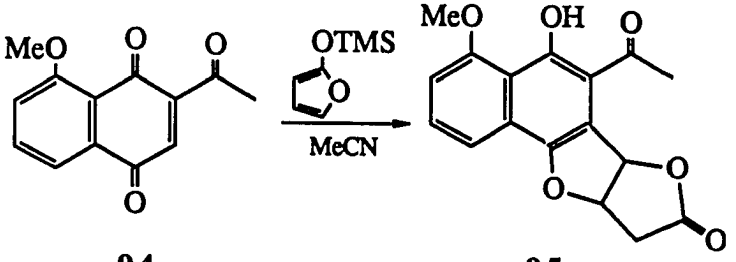
8-Methoxy-2-acetylnaphthoquinone **94** also gave the pyranonaphthoquinone product **96** which should be easily converted to kalafungin.



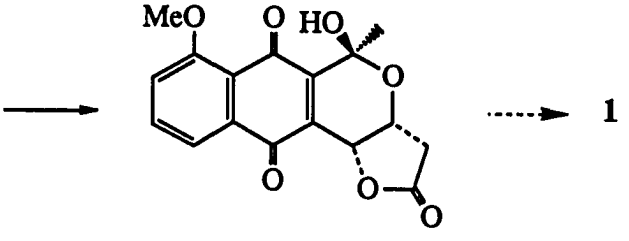
90 88



92 93

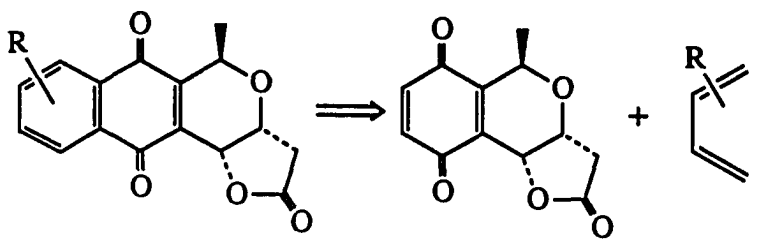


94 95



96

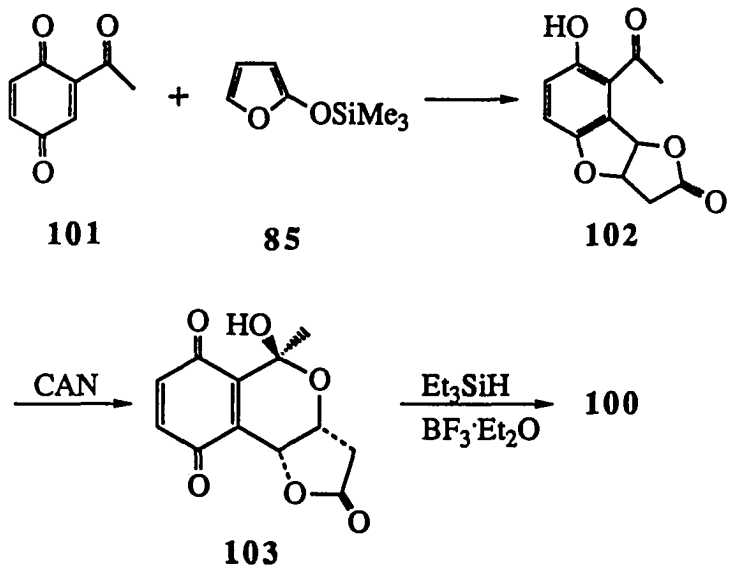
Our new synthetic approach stemmed from careful analysis of the structure of pyranonaphthoquinones. Nanaomycin A (**3**), frenolicin (**9**), kalafungin (**1**), medermycin (**11**) mederrhodin (**12**), and novel C-glycoside SCH 38519 (**17**) are representives of pyranonaphthoquinone antibiotics. They not only show similar biological activities, but also have in common the isochromanquinone skeleton as was mentioned before. It is clear from an examination of their structures that the primary difference lies in the substitution pattern on the naphthoquinone subunit. Our interest in developing a common intermediate for all of these natural products led us to plan the route shown below.



100

A direct route to **100**, coupled with the annulation methodology developed by Bauman et al.,[50] could provide a general synthesis of these pyranonaphthoquinone antibiotics.

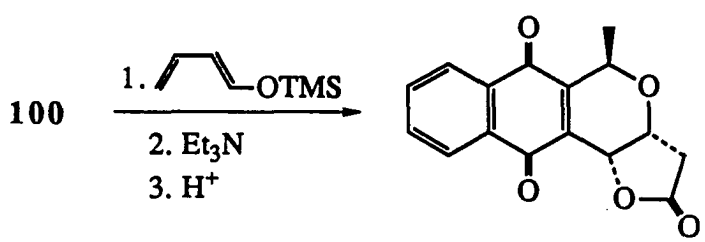
It is apparent that the versatile intermediate **100** could be prepared from acetylbenzoquinone **101**. In fact, **101** reacted with **85** in dichloromethane to give the cyclization product **102**, which was oxidized with ceric ammonium nitrate to the provided hemiketal **103**. The compound **100** was obtained by reduction of hemiketal **103** using triethylsilane and boron trifluoride etherate.



101 85 102

103

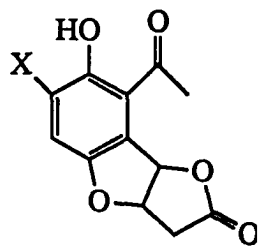
Initially, quinone **100** reacted with 1-trimethylsilyloxy-1,3-butadiene, The resulting Diels-Alder adduct was treated with triethylamine, followed by acidic work up, to provide 9-deoxykalafungin.



93

However, we met with difficulty when **100** reacted with 1- methoxy-1-(trimethylsilyloxy)butadiene under similar conditions. The expected product, kalafungin, could not be separated. As a result, a mixture of two regioisomers was obtained in low yield.

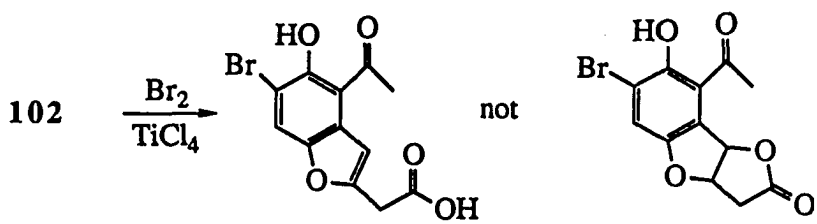
In order to achieve good regioselectivity, the intermediate **104** was prepared. Group X could be a phenylthio group or a halogen atom.



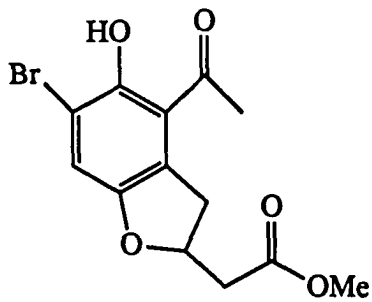
104

Introduction of a phenylthio group by treatment of **102** with PhSCl and base (Et_3N or NaH) did not give the desired product.

Bromination of o-hydroxyacetylphenol using bromine/$TiCl_4$ has been shown to be selective for bromination ortho to the phenol.[51] Bromination of **102** with 1 equivalent of bromine gave the bromination product **105**. This result did not give us the desired product. However, it did suggest the versatile intermediate **106**, instead of **104**.

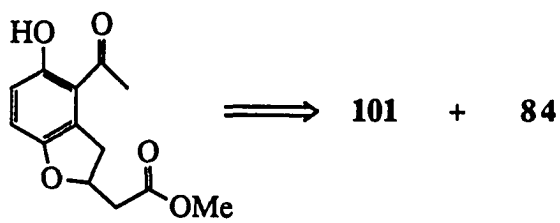


105



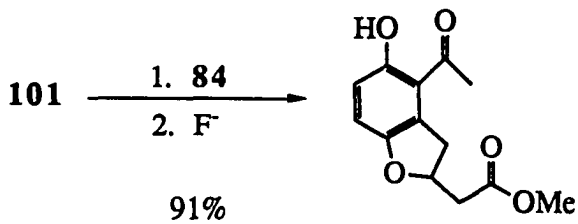
106

An acid such as nanaomycin A can be converted into a lactone in high yield under mild conditions.[52] Previous work in this laboratory has shown that activated naphthoquinones react with activated 1,3-butadienes to give cyclization products in high yields. We expected that the reaction of acetylbenzoquinone with 1-methoxy-1-(trimethylsilyioxy)butadiene should give the cyclization product also.



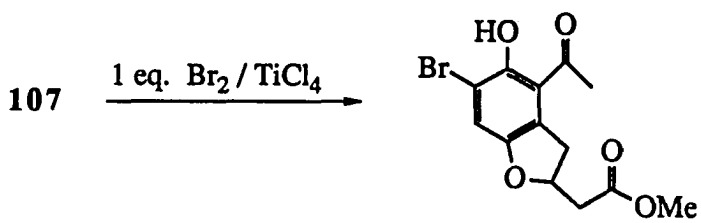
101 + **84**

In fact, ester **107** was obtained from acetylbenzoquinone via the one-pot Diels-Alder-retro-Claison (DARC) reaction in 91% yield.

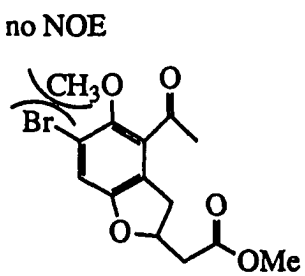


107

Bromination of **107** with 1 equivalent of bromine afforded only the bromophenol **108**, as evidenced by TLC and the proton NMR spectrum of the unpurified material. Support for the regiochemical assignment came from an NOE study of the methyl ether of **108**. Irradiation of the methyl group of the ether did not cause an enhancement of the aromatic ring proton, which is consistent with the structure of **108**.

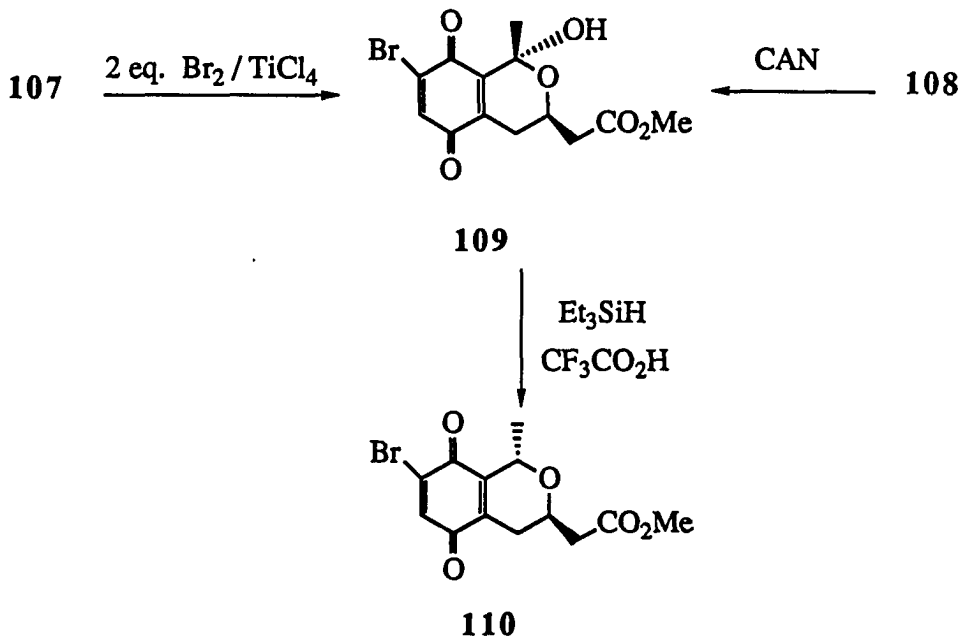


108

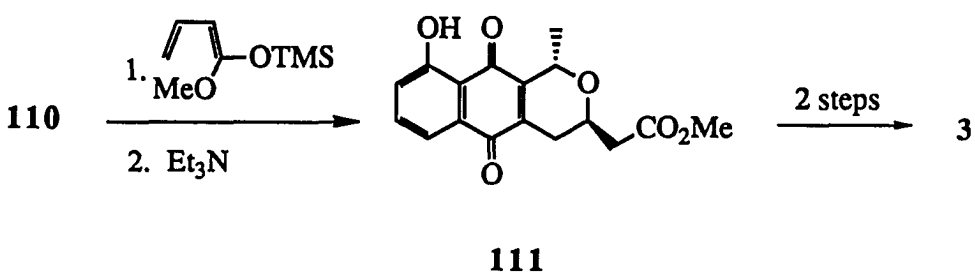


Interestingly, bromination and oxidation with 2 equivalent of bromine and $TiCl_4$ in methylene chloride at 0°C afforded quinone **109** (which can also be

made by oxidition of **108** with ceric ammonium nitrate) in 82% yield, presumably via the intermediacy of bromophenol **108.**

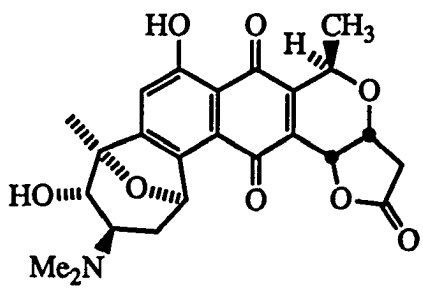


Initially, quinone **109** was treated with 1-methoxy-1-(trimethylsilyloxy)-butadiene at -78°C to afford a complex product mixture as evidenced by thin layer chromatography. Fortunately, reductive removal of the hydroxyl group provided the quinone **110**, which did react to yield **111,** an advanced intermediate in our previous synthesis of nanaomycin A.



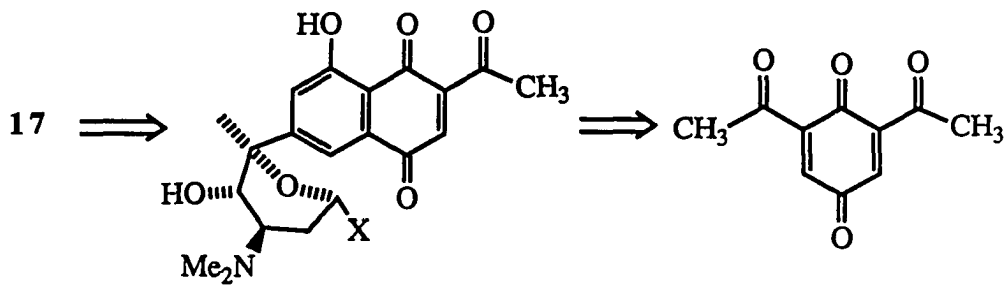
The sequence **107 -- 109 -- 110** produced a common intermediate by which the more complex pyranonaphthoquinones can be prepared. Since highly oxygenated dienes are readily available, this extremely convergent approach will permit the direct synthesis of biologically active analogues and may also aid in the structure identification of quinone natural products.

Our next effort involved the synthesis of the interesting novel C-glycoside SCH 38519 (**17**).

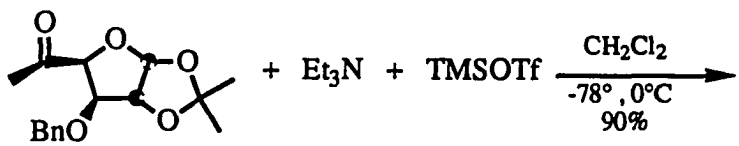


17

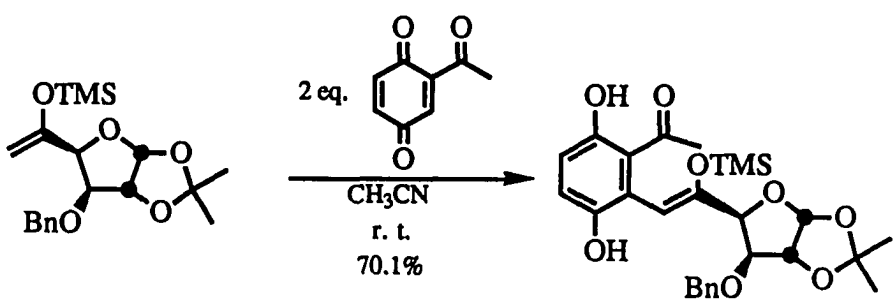
In the context of extending the DARC reaction and our three step lactone formation strategy, we recognized the need for a synthesis of aryl C-glycosyl compounds based on a Michael addition/aldol condensation sequence. This sequence would provide an aryl C-glycosyl compound with the phenol group meta to the C-glycosyl linkage. In contrast, the synthetic approaches developed by Kozikowski et al.,[53] Cai and Qiu,[54] Hoffmann and Schmidt,[55] Martin and Horton[56] produced the C-glycosyl compound with a phenol in the ortho or para position. If such a sequence could be realized, a retrosynthetic analysis for compound **17** might be devised as shown below.



In order to test this question, we reacted the enol silyl ether of **112** with acetylbenzoquinone, expecting to obtain a diketone. The product we actually isolated in 70% yield was enol silyl ether **113**. Surprisingly, all attempts to cyclize **114** to a naphthol led to the recovery of **114** (t-BuOK in THF or DMF, 25°C) or to the decomposition of **114** (t-BuOK in DMF, 60°C; NaOMe/MeOH, 25°C).

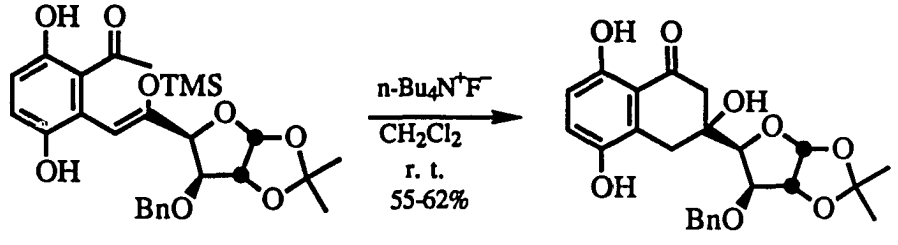


112

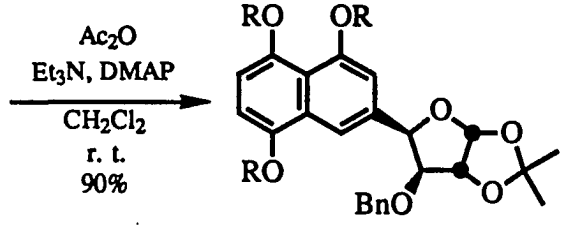


113 **114**

However, the deprotection of the enol silyl ether **114** with commercially available tetra-n-butylammonium fluoride in methylene chloride unexpectedly produced the hydroxyketone **115** in 62% yield. We had anticipated that the hydroxyketone would rapidly dehydrate to form the aromatic ring. The structure of **115** was supported by CMR resonances at 201.69 and 156.15. The proton NMR spectrum exhibited three AB quartets for the three methylene groups in **115**. This reaction has been repeated 3 times with yields ranging from 55% to 62%. The reaction of hydroxy ketone **115** with acetic anhydride, triethylamine and 4-dimethylaminopyridine (DMAP) afforded triacetate **116** (R = $COCH_3$) in 90% yield.

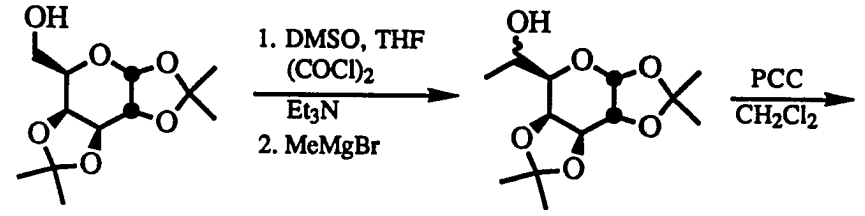


114 **115**

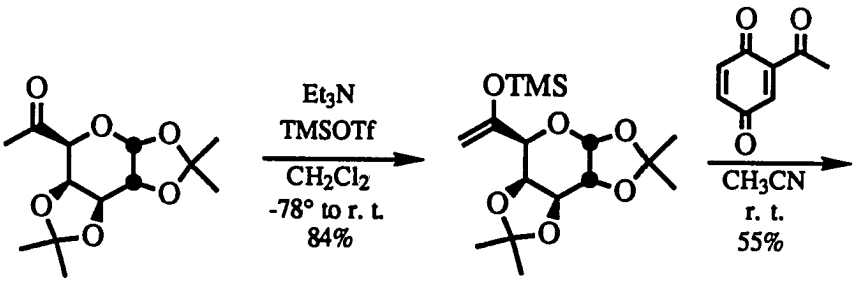


116

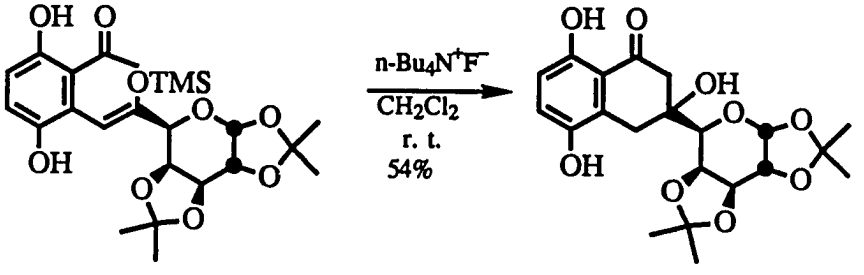
The conversion of ketone **112** into triacetate **116** demonstrated that the Michael addition/aldol condensation sequence was a viable one for the generation of C-glycosyl compounds. In compound **17** there are two bonds from



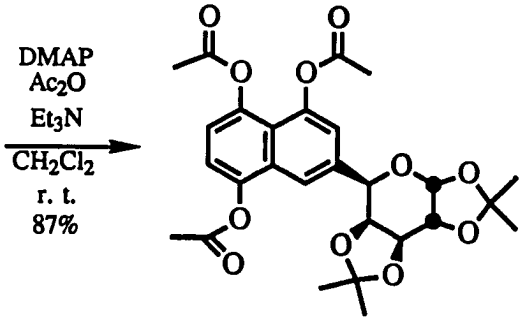
117 118



119 120



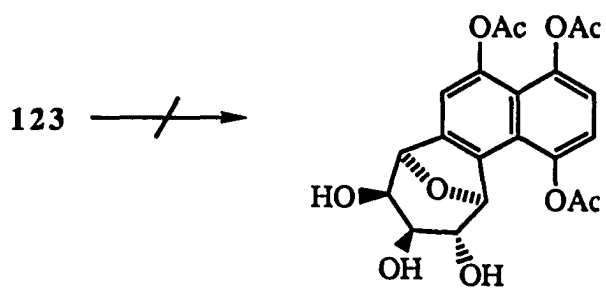
121 122



123

the carbohydrate unit to the naphthoquinone ring. In the hope of achieving the second linkage on a model system which more closely resembled a precursor to **17**, we prepared pyranose **119** from the readily available bis-acetonide **117** by a two-pot reaction. The enol silyl ether was then generated by the reaction of **119** with triethylamine and trimethylsilyl triflate. Enol silyl ether **120** reacted with acetylbenzoquinone to afford a 55% isolated yield of adduct **121**. This compound was treated with tetra-n-butylammonium fluoride in methylene chloride to afford keto alcohol **122** in 54% yield. The naphthalene **123** was generated by reaction of **122** with acetic anhydride, triethylamine and DMAP in 87% yield.

The cyclization of pyranose **123** was examined. Despite extensive variation of temperature, Lewis acid (PTSA/MeCN, 25°C to 80°C; $SnCl_4$, 0°C, 25°C; Amberlite IR-20/THF, 25°C to 70°C) and order of addition, no cyclized products such as **124** were obtained. Attempts to selectively cleave the 1,2-acetonide(Ac_2O, AcOH, H_2SO_4) resulted in the decomposition of **123**.



124

The methodology described herein offers an attractive new pathway for the synthesis of aromatic C-glycosyl compounds which would be difficult to prepare

by previously reported methods. The three-step sequence of Michael addition, aldol condensation and aromatization is compatible with a variety of functional groups on both the carbohydrate portion and the quinone portion. The preparation of the requisite carbohydrate and quinone units for the total synthesis of **17** will be continued in this laboratory.

EXPERIMENTAL

Unless otherwise noted, materials were obtained from commercial suppliers and were used without purification. THF and diethyl ether were distilled from sodium benzophenone ketyl under nitrogen prior to usage. Benzene was distilled from lithium aluminum hydride. Dichloromethane was distilled from calcium hydride. Unless otherwise noted, all reactions were conducted under an argon atmosphere and all organic extracts were dried over anhydrous magnesium sulfate. H:EA refers to hexanes:ethyl acetate solvent mixtures for TLC. The purity of all title compounds was determined to be >90% by proton NMR spectroscopy and/or elemental analysis. Melting points were determined on a Fisher-Johns melting point apparatus and are uncorrected. Infrared spectra were obtained on an IBM IR-90 Series FT IR spectrophotometer. High field (300 MHz) proton spectra were obtained with a Nicolet Magnetics Corporation NT-300 spectrometer. All chemical shifts are reported in δ relative to tetramethylsilane as an internal standard. Coupling constant (J) are reported in Hz. Abbreviations: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet. Carbon-13 NMR spectra were determined on a Nicolet NT-300 soectrometer and are reported in ppm relative to the central peak of $CDCl_3$ (77.06 ppm). High resolution mass spectra were recorded on a Kratos model MS-50 spectrometer. Low-resolution mass spectra were recorded on a Finnegan 4023 mass spectrometer. Silica gel used for flash chromatography was 230-400 mesh (Kieselgel 60) purchased from EM Science. Gravity column chromatography was performed on 60-200 mash silica gel purchased from Davison Chemical (WR Grace Inc.). Elemental analyses were performed by Galbraith Laboratories, Inc.

General Procedure for the Photolysis Experiments

A solution of 2-ethoxy-1,4-naphthoquinone (1 equiv.) and the alkenol (2 equiv.) in benzene (0.05 M) in a quartz tube under a nitrogen atmosphere was irradiated until 90% completion using a medium pressure mercury arc lamp. The solution was then concentrated in vacuo and purified by chromatography on silica gel using 15:10:1 hexanes:ethyl acetate:ethanol.

74 NMR ($CDCl_3$): 1.387 (d, J = 6.6 Hz, 3 H), 2.198-2.004 (m, 5 H), 2.943 (m, 1 H), 3.066 (bs, 1 H), 3.507 (m, 1 H), 3.651 (m, 1 H), 3.907 (m, 1 H), 4.726 (s, 1 H), 4.805 (q, J = 6.3 Hz, 1 H), 8.032-7.410 (m, 4 H). IR (neat) 781, 1032, 1051, 1121, 1259, 1294, 1325, 1597, 1663, 2990, 3290, 3476 cm^{-1}. MS: m/e 256, 230, 212, 197, 184, 173, 159, 143, 128, 115, 77. HRMS: m/e for $C_{16}H_{19}O_4$: calcd. 275.12834, measured 275.12865. CMR ($CHCl_3$) 197.502, 143.475, 134.557, 129.106, 128.322, 127.253, 126.019, 88.037, 86.845, 71.860, 61.335, 48.674, 36.523, 31.943, 24.934, 15.156. TLC (20:10:1 H:EA:ethanol) R_f = 0.13.

75 NMR ($CDCl_3$): 1.491 (d, J = 6.3 Hz, 3 H), 1.897 (m, 1 H), 2.096 (m, 1 H), 2.568 (dd, J = 4.5, 3.0 Hz, 1 H), 3.069 (m, 1 H), 3.087 (s, 1 H), 3.550 (m, 1 H), 3.879 (m, 1 H), 3.990 (m, 1 H), 4.851 (q, J = 6.3 Hz, 1 H), 8.07-7.46 (m, 4 H). IR (neat) 762, 785, 1092, 1121, 1283, 1329, 1597, 1663, 2981, 3327, 3431 cm^{-1}. MS: m/e 242, 216, 198, 181, 160, 143, 128, 115, 105, 77. HRMS: m/e for $C_{15}H_{14}O_3$: calcd. 242.09430, measured 242.09455. CMR ($CHCl_3$) 196.864, 143.226, 134.848, 129.743, 128.863, 127.610, 126.173, 89.173, 87.438, 71.304, 62.227, 48.827, 39.244, 21.259, 16.158. TLC (20:10:1 H:EA:ethanol) R_f = 0.16.

Furo[2.3-b]naphtho[2.3-d]furan-4-(1-oxobutyl)--6b.8.9.9a-tetrahydro-5-hydroxy-8-one 88

To a solution of 2-butyrylnaphthyhydroquinone (2.3 g, 10 mmol) in 100 ml of acetonitrile at room temperature was added ceric ammonium nitrate (12.6 g, 23 mmol) in 10 ml of water. After 10 minutes, the reaction was complete as evidenced by thin layer chromatography. The mixture was poured onto 30 ml of pH 7.2 buffer and the aqueus layer extracted twice with methylene chloride. The organic layer was dried, filtered and concentrated in vacuo. To the crude quinone in 50 ml of dry methylene chloride at -78^{0}C was added dropwise 2-trimethylsilyloxyfuran (1.87 g, 12 mmol). After 1 hour, the solvent was removed and the crude product chromatographed on silica gel (3:1 hexane : ethyl acetate) to afford 1.82 g (58% yield) of keto phenol. ^{1}H NMR ($CDCl_3$): 1.067 (t, 3 H, J = 7.5 Hz), 1.846 (m, 2 H), 3.008 (dt, 1 H, J = 17.7, 7.2 Hz), 3.179 (d, 2 H, J = 3.9Hz), 3.287 (dt, 1 H, J =1 7.7, 7.2 Hz), 5.539 (dt, 1 H, J = 6.3, 3.9 Hz), 6.461 (d, 1 H, J = 6.0 Hz), 7.675 (m, 2 H), 7.933 (m, 2 H), 8.503 (m, 1 H), 14.741 (s, 1 H). HRMS calcd for $C_{18}H_{16}O_5$: calcd. 312.09978, found 312.09966. MS: m/e 312, 294, 279, 269, 249, 237, 225, 196, 167, 139, 97, 69, 55. IR (neat) 3422, 2970, 1784, 1761, 1616, 1450, 1335, 1146, 1047, 908 cm^{-1}.

3.3a.5.11b-Tetrahydro-5-hydroxy-5-propyl-2H-furo[3.2-b]naphtho[2.3-d]pyran-2.6.11-trione 89

To a slurry of the keto phenol prepared above (1.65 g, 5.29 mmol) in 70 ml of acetonitrile at room temperature was added dropwise a solution of ceric ammonium nitrate (7.2 g, 13.2 mmol) in 7 ml of water. After 15 minutes the solution was poured into pH 7.2 buffer (20 ml) and then diluted with 100 ml of

water. The reaction was extracted twice with methylene chloride. The organic layer was dried, filtered and concentrated to provide 1.70 g (98% yield) of pure quinone. ^{1}H NMR ($CDCl_3$): 0.851 (t, 3 H, J = 7.5 Hz), 1.056 (m, 1 H), 1.387 (m, 1 H), 1.984 (m, 1 H), 2.316 (m, 1 H), 2.760 (d, 1 H, J = 17.4 Hz), 2.949 (dd, 1 H, J = 4.8, 17.4 Hz), 3.207 (s, 1 H), 4.887 (dd,1 H, J = 3.0, 4.5 Hz), 5.298 (d, 1 H, J = 2.7 Hz), 7.320 (m, 2 H), 8.148 (m, 2 H). HRMS calcd for $C_{18}H_{16}O_6$: 328.09469, found 328.09462. MS: m/e 328, 310, 285, 258, 240, 225, 197, 187, 105, 77, 69, 55. IR: (neat) 3428, 2970, 1771, 1670, 1593, 1285, 1165, 1045, 893, 735 cm^{-1}.

9-Deoxyfrenolicin B 10

To a solution of the quinone prepared above (1.05 g, 3.2 mmol) in 80 ml of methylene chloride at -78°C was added triethylsilane (1.10 ml, 6.91 mmol), followed by the dropwise addition of boron trifluoride etherate (0.55 ml, 4.5 mmol). The reaction was stirred at methylene chloride and the aqueous layer extracted again with methylene chloride. The organic layer was dried, filtered and concentrated. The crude product was recrystallized from ethyl ether to afford 0.85 g (85% yield) of product. ^{1}H NMR ($CDCl_3$): 1.022 (t, 3 H, J = 7.2 Hz), 1.662 (m, 4 H), 2.709 (d, 1 H, J = 17.7 Hz), 2.968 (dd, 1 H, J = 5.4, 17.7 Hz), 4.630 (dd, 1 H, J = 3.0, 5.1 Hz), 4.910 (dd, 1 H, J = 3.0, 10.2 Hz), 5.292 (d, 1 H, J = 3.0 Hz), 7.785 (m, 2 H), 8.131 (m, 2 H). HRMS calcd for $C_{18}H_{16}O_5$: 312. 09978, found 312.09922. MS: m/e 312, 284, 270, 241, 225, 221, 197, 115, 105, 77. IR (film) 2950, 2920, 2850, 1785, 1770, 1650, 1595, 1455, 1355, 1200, 1150, 890 cm^{-1}.

4-Acetyl-5-hydroxy-6-bromobenzofuran-2-yl acetic acid **105**

The 0.64 ml of $TiCl_4$ (1.0 M in CH_2Cl_2) solution was added to a stirred solution of the keto phenol **102** (60 mg, 0.256 mmol) in 3 ml of methylene chloride, followed by addition of 0.26 ml of 1.0 M bromine in carbon tetrachloride. The solution was stirred for 10 min. at room temperature, then poured into ice water and stirred rapidly. The aqueous layer was extracted with methylene chloride. The organic layer was washed with brine, dried over magnesium sulfate. The crude product was chromatographed on silica gel (2:1 ethyl acetate : hexanes) to afford 66 mg (85% yield) of a yellow solid of bromoketone with m.p. 164-166°C. ^1H NMR (CD_3COCD_3): 2.844 (s, 3 H), 3.974 (s, 2 H), 5.815 (s, 1 H), 7.153 (s, 1 H), 8.073 (s, 1 H), 13.724 (s, 1 H). MS m/e 314, 312, 299, 297, 269,267, 145,89, 53, 43. HRMS calcd for $C_{12}H_9O_5Br$: 311.96354, found 311.96333. IR: (neat) 3439, 3069, 2920, 1720, 1620, 1418, 1373, 1335, 1221, 1024, 982, 812 cm^{-1}.

Methyl 4-acetyl-2,3-dihydro-5-hydroxybenzofuran-2-yl acetate **107**

To a solution of acetylbenzoquinone (2.30 g, 15.3 mmol) in 60 mL of dry CH_2Cl_2 at -78°C was added 1-t-butyldimethylsilyloxy-1-methoxybutadiene (6.52 g, 30.6 mmol). The solution was stirred at -78°C for 30 min and then allowed to warm to ambient temperature for 1 h. The solution was cooled to 0°C and 40 mL of acetonitrile, 20 mL of pH 7.2 phosphate buffer and 35 mL of tetra-n-butyl-ammonium fluoride (1 M in THF) was added. The solution was allowed to warm to ambient temperature and acidified with 3N HCl. The aqueous layer was extracted twice with CH_2Cl_2. The combined organic layers were dried, concentrated and then purified by flash chromatography using 3:1 hexanes:ethyl

acetate to provide 3.49 g (91% yield) of phenol **107**. Phenol **107** was a clear liquid. HRMS calcd for $C_{13}H_{14}O_5$: 250.08413, found 250.08439. IR (film) 3020, 1736, 1580, 1474, 1215, 827 cm^{-1} . MS: m/e 250, 219, 177, 161, 131, 91. ^1H NMR ($CDCl_3$): 2.58 (s, 3 H), 2.72 (dd, J = 16.2, 6.6 Hz, 1 H), 2.91 (dd, J = 16.2, 6.3 Hz, 1 H), 3.23 (dd, J = 16.2 7.2 Hz, 1 H), 3.71 (dd, J = 16.5, 8.7 Hz, 1 H), 3.74 (s, 3 H), 5.17 (m, 1 H), 6.79 (d, J = 9.0 Hz, 1 H), 6.95 (d, J = 9.0 Hz, 1 H), 12.16 (s, 1 H). TLC (3:1 H:EA) R_f = 0.30.

Methyl 4-acetyl-2,3-dihydro-5-hydroxy-6-bromobenzofuran-2-yl acetate **108**

To a solution of phenol **107** (1.50 g, 6.0 mmol) in 30 ml of CH_2Cl_2 at room temperature was added 15 ml of a 1.0 M solution of $TiCl_4$ in CH_2Cl_2, followed by bromine (0.948 g, 6.0 mmol). The solution was stirred overnight. Cool water (10 mL) was carefully added and the aqueous layer was extracted with CH_2Cl_2 . The combined organic layers were washed with saturated $NaHCO_3$ solution and then with brine. The organic layer was dried and concentrated. The crude product was purified by flash chromatography using 3:1 hexanes: ethyl acetate to provide 1.258 g (63.5% yield) of **108**. HRMS calcd for $C_{13}H_{13}BrO_5$: 327.99463, found 327.99398. IR (film) 3069, 3022, 1726, 1636, 1590, 1433, 1244, 1167, 1020, 853 cm^{-1}. MS: m/e 330, 328, 297, 269, 239, 211, 176, 147, 118,91. ^1H NMR ($CDCl_3$): 2.61 (s, 3 H), 2.73 (dd, 1 H, J = 16.0, 6.6 Hz), 2.90 (dd, 1 H, J = 16.0, 6.6 Hz), 3.21 (dd, 1 H, J = 16.0, 7.2 Hz), 3.69 (dd, 1 H, J = 16.5, 9.0 Hz), 3.74 (s, 3 H), 5.19 (m, 1 H), 7.25 (s, 1 H), 12.71 (s, 1 H). TLC (3:1 H:EA) R_f = 0.52.

cis-Methyl 7-bromo-3,4 dihydro-5,8-dioxo-1-methyl-1H-2-benzopyran-3-yl acetate **110**

To a solution of phenol **107** (0.75 g, 3.0 mmol) in 15 mL of CH_2Cl_2 at 25°C was added 10.5 mL of a 1 M solution of $TiCl_4$ in CH_2Cl_2 , followed by bromine (0.948 g, 6.0 mmol). The solution was stirred for 1.5 h. Water (10 mL) was carefully added and the aqueous layer was extracted with CH_2Cl_2 . The combined organic layers were washed with saturated $NaHCO_3$ solution and then with brine. The organic layer was dried and concentrated. The crude product was purified by flash chromatography using 3:1 hexanes: ethyl acetate to provide 0.85 g (82% yield) of **109**. HRMS calcd for $C_{13}H_{13}BrO_5$: 345.98751, found 345.98707. IR (film) 3425, 3020, 1738, 1674, 1659,1595, 1439, 1267 cm^{-1}. ^1H NMR ($CDCl_3$): 1.74 (s, 3 H), 2.25 (dd, 1 H, J = 18.9, 11.1 Hz), 2.61 (dd, 1 H, J = 15.9, 5.7 Hz), 2.69-2.78 (m, 2 H), 2.97 (s, 1 H), 3.73 (s, 3 H), 4.46 (m, 1 H), 7.30 (s, 1 H). MS: m/e 346, 344, 328, 284, 269, 255, 227, 224, 135, 103, 82, 71, 53. TLC (3:1 H:EA) R_f = 0.17.

In practice, **109** was reduced directly to afford **110**. To a solution of **109** (0.280 g, 0.81 mmol) at -78°C in 8 mL of CH_2Cl_2 was added triethylsilane (0.174 g, 1.5 mmol) followed by $BF_3{\cdot}Et_2O$ (0.1 mL). After 30 min, the reaction was warmed to 25°C and the solvent was removed. The crude product was immediately purified by flash chromatograpy using 3:1 hexanes:ethyl acetate to afford a 95% yield of **110**. Quinone **110** was an oil. HRMS calcd for $C_{13}H_{13}BrO_5$: 327.99463, found 327.99502. IR (film) 3061, 2982, 1738, 1668, 1655, 1595, 1259 cm^{-1}. ^1H NMR ($CDCl_3$): 1.47 (d, J = 6.6 Hz, 3 H), 2.24 (ddd, J = 18.3, 10.4, 4.0 Hz, 1 H), 2.58 (dd, J = 15.8, 5.7 Hz, 1 H), 2.66-2.75 (m, 2 H), 3.73 (s, 3 H), 3.85-3.94 (m, 1 H), 4.69-4.78 (m, 1 H), 7.26 (s, 1 H). MS: m/e 330,

328, 298, 296, 255, 241, 227, 176, 148, 119, 91, 79, 65. TLC (3:1 H:EA) R_f = 0.17.

cis-Methyl 3,4-dihydro-5,10-dioxo-9-hydroxy-1-methyl-1H-naphtho[2,3-c]pyran-3-yl acetate **111**

To a solution of **110** (0.098 g, 0.3 mmol) in 5 mL of CH_2Cl_2 was added dropwise 1-trimethylsilyloxy-1-methoxy-1,3-butadiene (0.103 g, 0.6 mmol). The solution was stirred at -78°C for 1 h and then allowed to warm to ambient temperature. Triethylamine (0.070 g, 0.7 mmol) was added and the solution was stirred for 5 min. The solvent was removed in vacuo and the residue was dissolved in acetonitrile. A 5% solution of HF in acetonitrile was added and the solution was stirred for 5 min (TLC). The solvent was removed in vacuo and the residue was partitioned between water and CH_2Cl_2. The crude product was purified by silica gel chromatography using 5:1 hexanes:ethyl acetate to provide 0.032 g (34%) of **111**. This compound was identical to that produced in our previous synthesis. HRMS calcd for $C_{17}H_{16}O_5$: 300.0998, found: 300.0993. IR(film) 3018, 2990, 1742, 1663, 1624, 1595, 1296, 1215 cm-1. ^1H NMR (CDCl3): 1.54(d, J=6.6 Hz, 3H), 2.34(ddd, J=18.5, 10.5, 4.0 Hz, 1H), 2.63(dd, J=16.5, 5.4 Hz, 1H), 2.75(dd, J=15.6, 7.5 Hz, 1H), 2.88(dt, J=18.3, 2.7 Hz, 1H), 3.74(s, 3H), 3.91-3.99(m, 1H), 4.86-4.90(m, 1H), 7.71-7.79(m, 1H), 8.04-8.10(m, 1H). MS: m/e 316, 296, 284, 242, 227, 214, 197, 168, 139, 121, 92, 59. TLC(3:1 H:EA) Rf=0.47.

5-Acetyl-1,2:3,4-bis-O-(1-methylethylidene)-L-arabinopyranose **119**

To a stirred solution of oxalyl chloride (3.97 g, 31.3 mmol) in 50 mL of THF at -78°C was added dimethyl sulfoxide (3.26 g, 41.7 mmol). The solution was stirred at -78°C for 30 min. The diacetonide of galactose (5.43 g, 20.9 mmol) in 20 mL of THF was added. The solution was allowed to warm to 0°C for 30 min and then cooled to -78°C. Triethylamine (10.55 g, 104 mmol) was added and the solution was allowed to slowly warm to 25°C over 1 h. The solution was then cooled to -78°C and MeMgBr (3.0 M, 38.2 mL, 114 mmol) was added dropwise. After the reaction had stirred at -78°C for 2 h, it was allowed to warm to 25°C for 4 h. The solution was cooled to -78°C and quenched by the addition of 3 mL of EtOH, followed by 20 mL of NH_4Cl/NH_4OH buffer. The reaction mixture was poured into 300 mL of NH_4Cl/NH_4OH buffer and extracted twice with 300 mL of ether. The organic layer was dried over $MgSO_4$ and purified by silica gel chromatography with 1:1 H:EA. The purified alcohol **118** was dissolved in 150 mL of CH_2Cl_2. To this solution was added PCC (9.05 g, 42 mmol). The reaction was stirred for 36 h, diluted with ether, filtered and purified by silica gel chromatograpy with 2:1 H:EA to provide 5.02 g (88% yield) of ketone **119**. ^1H NMR ($CDCl_3$): 5.645 (d, 1 H, J = 5.1 Hz), 4.639 (dd, 1 H, J = 2.4, 8.7 Hz), 4.557 (dd, 1 H, J = 2.1, 7.5 Hz), 4.363 (dd, 1 H, J = 2.4, 5.1 Hz), 4.168 (d, 1 H, J = 2.1 Hz), 2.259 (s, 3 H), 1.505 (s, 3 H), 1.448 (s, 3 H), 1.342 (s, 3 H), 1.313 (s, 3 H). IR (neat) 1722, 1303, 1258, 1078, 1009, 922, 775 cm^{-1}. MS: m/e 272, 257, 229, 199, 171, 155, 141, 111, 97, 85, 71. HRMS: m/e for $C_{13}H_{26}O_6$ calcd. 272.12599, measured 272.12582. TLC (1:1 H:EA) R_f = 0.40.

5-(1-Trimethylsilyloxyethenyl)-1,2:3,4:bis-O-(1-methylethylidene)-L-arabinopyranose **120**

To a solution of **119** (0.650 g, 2.39 mmol) and Et_3N (0.315 g, 3.11 mmol) in 5 mL of CH_2Cl_2 at 0°C was added trimethylsilyl triflate (0.55 mL, 2.86 mmol). The solution was allowed to warm to 25°C over 4 h. The solution was diluted with CH_2Cl_2 and poured into brine. The brine was extracted twice with CH_2Cl_2. The organic layer was dried and concentrated in vacuo. The resulting oil was purified by silica gel chromatograpy with 10:1 H:EA to afford 0.690 g (84% yield) of enol silyl ether **120**.

General Procedure for the Enol Silyl Ether Additions to Acetylbenzoquinone

To a solution of acetylbenzoquinone (2 equiv.) in acetonitrile (0.25 M) at 25°C was added the enol silyl ether (1 equiv.) dissolved in MeCN. The reaction was allowed to stir at 25°C for 8 h. The solvent was removed in vacuo. The residue was dissolved in ether and washed with saturated $Na_2S_2O_3$. The ether layer was dried over $MgSO_4$, filtered and concentrated in vacuo. The product was purified by silica gel chromatography with 5:1 H:EA to afford the pure product.

5-(2-(2-Acetyl-3,6-dihydroxyphenyl)-1-trimethylsilyloxyethenyl)-1,2-O-(1-methylethylidene)-3-phenylmethoxy-L-threofuranose **114**

^1H NMR ($CDCl_3$): 12.185 (s, 1 H), 7.349 (s, 5 H), 6.974 (d, 1 H, J = 9 Hz), 6.775 (d, 1 H, J = 9 Hz), 5.991 (d, 1 H, J = 3.6 Hz), 4.728 (d, 1 H, J = 9.3 Hz), 4.630 (d, 1 H, J = 3.6 Hz), 4.548 (d, 1 H, J = 10.8 Hz), 4.544 (d, 1 H, J = 3.3 Hz), 4.106 (d, 1 H, J = 3.3 Hz), 3.893 (d, 1 H, J = 17.7 Hz), 3.121 (d, 1 H, J = 17.7 Hz),

1.549 (s, 3 H), 1.341 (s, 3 H), 0.069 (s, 9 H). IR (oil) 1639, 1464, 1620, 1209, 1126, 982, 937 cm^{-1}. MS: m/e 514, 424, 265, 237, 204, 147, 91, 73. HRMS: m/e for $C_{27}H_{34}O_8Si$ calcd. 514.20231, measured 514.20105. CMR ($CDCl_3$) 204.114, 157.862, 149.569, 137.470, 128.441, 127.987, 127.758, 126.123, 118.317, 117.335, 112.035, 112.006, 110.205, 105.699, 82.921, 82.651, 81.969, 73.017, 43.554, 31.083, 26.943, 26.374, 1.461. TLC (5:1 H:EA) R_f = 0.48.

5-(2-(2-Acetyl-3,6-dihydroxyphenyl)-1-trimethylsilyloxyethenyl)-1,2:3:4-bis-O-(1-methylethylidene)-L-arabinopyranose **121**

^1H NMR ($CDCl_3$) 12.200 (s, 1 H), 6.994 (d, 1 H, J = 8.7 Hz), 6.779 (d, 1 H, J = 9.0 Hz), 5.523 (d, 1 H, J = 4.8 Hz), 4.678 (dd, 1 H, J = 2.1, 8.1 Hz), 4.477 (dd, 1 H, J = 1.8, 8.1 Hz), 4.340 (dd, 1 H, J = 2.1, 4.8 Hz), 4.042 (d, 1 H, J = 1.8 Hz), 3.989 (s, 1 H), 1.602 (s, 3 H), 1.502 (s, 3 H), 1.393 (s, 3 H), 1.335 (s, 3 H), 0.153 (s, 9 H). IR (oil) 3030, 1634, 1450, 1254, 1051, 933, 845 cm^{-1}. MS: m/e 494, 479, 421, 265, 237, 204, 164, 73, 59. HRMS: m/e for $C_{24}H_{34}O_9Si$ calcd. 494.19722, measured 494.19675. CMR ($CDCl_3$) 204.013, 157.744, 150.119, 126.145, 118.314, 117.420, 117.115, 110.453, 108.139, 108.933, 108.762, 96.581, 70.894, 70.485, 69.818, 43.422, 31.031, 26.071, 25.817, 24.892, 24.149, 1.482. TLC (5:1 H:EA) R_f = 0.33.

General Procedure for the Aldol Condensation

To a solution of ketone (1 equiv.) in CH_2Cl_2 (0.1 M) was added tetra-n-butylammonium fluoride (1.0 M in THF, 1 eq.). The solution was stirred at 25°C for 8 h. The solution was concentrated in vacuo. The product was purified by chromatography on silica gel with 1:1 H:EA.

5-(1,2,3,4-Tetrahydro-2,5,8-trihydroxy-4-oxo-2-naphthyl)-1,2-O-(1-methylethylidene)-3-phenylmethoxy-L-threofuranose **115**

^{1}H NMR ($CDCl_3$): 11.682 (s, 1 H), 7.387 (m, 5 H), 6.819 (d, 1 H, J = 8.7 Hz), 6.625 (d, 1 H, J = 8.7 Hz), 6.082 (d, 1 H, J = 3.9 Hz), 4.757 (d, 1 H, J = 11.4 Hz), 4.690 (d, 1 H, J = 3.9 Hz), 4.551 (d, 1 H, J = 11.4 Hz), 4.211 (d, 1 H, J = 3.3 Hz), 4.010 (d, 1 H, J = 3.3 Hz), 3.500 (dd, 1 H, J = 1.8 Hz), 2.809 (d, 1 H, J = 1.8 Hz), 2.750 (s, 1 H), 2.702 (d, 1 H, J = 1.8 Hz), 1.472 (s, 3 H), 1.353 (s, 3 H). IR (oil) 3460, 2970, 2830, 1637, 1485, 1446, 1298, 1113, 870, 707 cm^{-1}. MS: m/e 442, 333, 275, 229, 192, 129, 113, 91, 69. HRMS: m/e for $C_{24}H_{26}O_8$ calcd. 442.16278, measured 442.16250. CMR ($CDCl_3$) 201.690, 156.151, 145.723, 135.442, 128.985, 128.878, 128.380, 125.153, 124.972, 115.874, 115.620, 112.006, 101.835, 82.777, 82.118, 81.365, 73.733, 72.252, 47.555, 33.207, 26.742, 26.186. TLC (1:1 H:EA) R_f = 0.49.

5-(1,2,3,4-Tetrahydro-2,5,8-trihydroxy-4-oxo-2-naphthyl)-1,2:3,4-bis-O-(1-methylethylidene)-L-arabinopyranose **122**

^{1}H NMR ($CDCl_3$) 11.737 (s, 1 H), 6.934 (d, 1 H, J = 8.7 Hz), 6.679 (d, 1 H, J = 9.0 Hz), 5.648 (d, 1 H, J = 4.8 Hz), 4.629 (dd, 1 H, J = 2.1, 8.1 Hz), 4.506 (dd, 1 H, J = 2.1, 8.1 Hz), 4.333 (dd, 1 H, J = 2.1, 4.8 Hz), 4.046 (s, 1 H), 3.669 (s, 1 H), 3.159 (s, 2 H), 3.027 (s, 2 H), 1.510 (s, 3 H), 1.381 (s, 3 H), 1.280 (s, 3 H), 1.124 (s, 3 H). IR (oil) 3508, 3221, 1639, 1591, 1462, 1375, 1167, 771 cm^{-1}. MS: m/e 422, 407, 364, 346, 288, 204, 193, 176, 150, 71, 59. HRMS: m/e for $C_{21}H_{26}O_9$ calcd. 422.15769, measured 422.15738. CMR ($CDCl_3$) 202.625, 156.109, 146.046, 125.404, 115.795, 115.569, 110.057, 108.884, 96.587, 74.879, 71.345,

70.934, 70.342, 68.900, 48.143, 31.999, 25.805, 25.682, 24.834, 23.966. TLC (2:1 H:EA) R_f = 0.55. This compound was a yellow solid with m.p. 195-196 °C.

General Procedure for Aromatization

To a solution of aldol (1 equiv.) in CH_2Cl_2 (0.1 M) was added Et_3N (10 equiv), acetic anhydride (8 equiv.) and a small crystal of DMAP. The reaction was stirred for 8 h. The solution was diluted with CH_2Cl_2 and poured into brine. The brine was extracted twice with CH_2Cl_2. The organic layer was dried and concentrated in vacuo. The product was purified by silica gel chromatography with 1:1 H:EA.

5-(4,5,8-Triacetoxy-2-naphthyl)-1,2-O-(1-methylethylidene)-3-phenylmethoxy-L-threofuranose **116**

^{1}H NMR ($CDCl_3$) 7.808 (s, 1 H), 7.276 (d, 1 H, J = 8.4 Hz), 7.142 (m, 5 H), 6.894 (d, 1 H, J = 6.9 Hz), 6.888 (d, 1 H, J = 7.8 Hz), 6.140 (d, 1 H, J = 3.6 Hz), 5.360 (d, 1 H, J = 3.0 Hz), 4.723 (d, 1 H, J = 3.9 Hz), 4.262 (d, 1 H, J = 12 Hz), 4.162 (d, 1 H, J = 12 Hz), 4.066 (d, 1 H, J = 3.0 Hz), 2.430 (s, 3 H), 2.400 (s, 3 H), 2.366 (s, 3 H), 1.569 (s, 3 H), 1.379 (s, 3 H). IR (oil) 3032, 2924, 2854, 1761, 1614, 1464, 1375, 1202, 951, 1078, 1022, 887, 744, 698 cm^{-1}. MS: m/e 550, 508, 466, 442, 424, 257, 204, 91. HRMS: m/e for $C_{30}H_{30}O_{10}$ calcd. 550.18391, measured 550.18498. TLC (1:1 H:EA) R_f = 0.46. Aanl. calcd for $C_{30}H_{30}O_{10}$: C, 65.49; H, 5.50. Found: C, 65.48; H, 5.58. This compound was a white solid with m.p. 153-154 °C.

5-(4,5,8-Triacetoxy-2-naphthyl)-1,2:3,4-bis-O-(1-methylethylidene)-L-arabinopyranose **123**

NMR ($CDCl_3$) 7.327 (s, 1 H), 7.270 (d, 1 H, J = 9.0 Hz), 7.255 (s, 1 H), 7.084 (d, 1 H, J = 8.1 Hz), 5.730 (d, 1 H, J = 4.8 Hz), 4.997 (s, 1 H), 4.731 (dd, 1 H, J = 2.1, 7.8 Hz), 4.476 (d, 1 H, J = 7.8 Hz), 4.420 (dd, 1 H, J = 2.1, 4.8 Hz), 2.441 (s, 3 H), 2.374 (s, 6 H), 1.581 (s, 3 H), 1.434 (s, 3 H), 1.332 (s, 3 H), 1.276 (s, 3 H). IR (oil) 1763, 1614, 1460 cm^{-1}. MS: m/e 530, 488, 446, 404, 346, 204, 113, 85, 59. HRMS: m/e for $C_{27}H_3O_{11}$ calcd. 530.17882, measured 530.17885. TLC (1:1 H:EA) R_f = 0.42. Anal. calcd for $C_{27}H_{30}O_{11}$: C, 61.17; H, 5.70. Found: C, 61.16; H, 5.84. This compound was a white solid with m.p. 234-235 °C.

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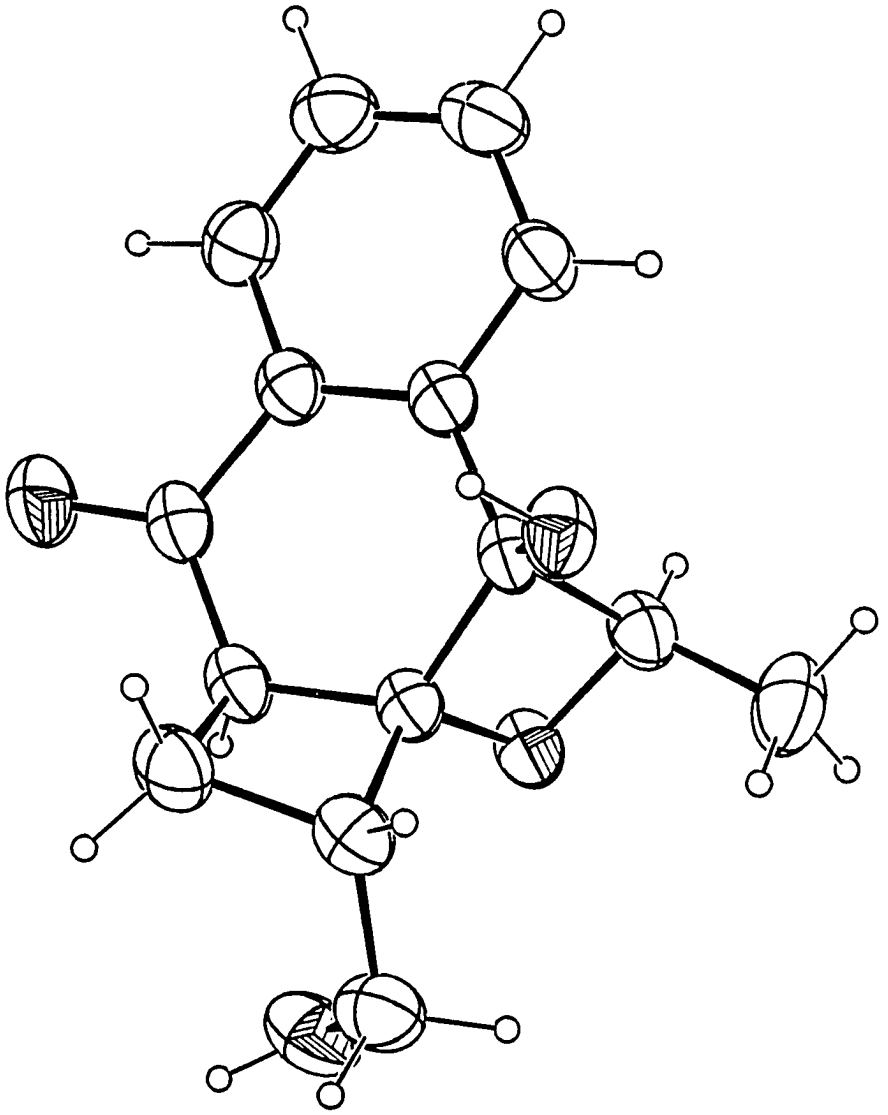
APPENDIX

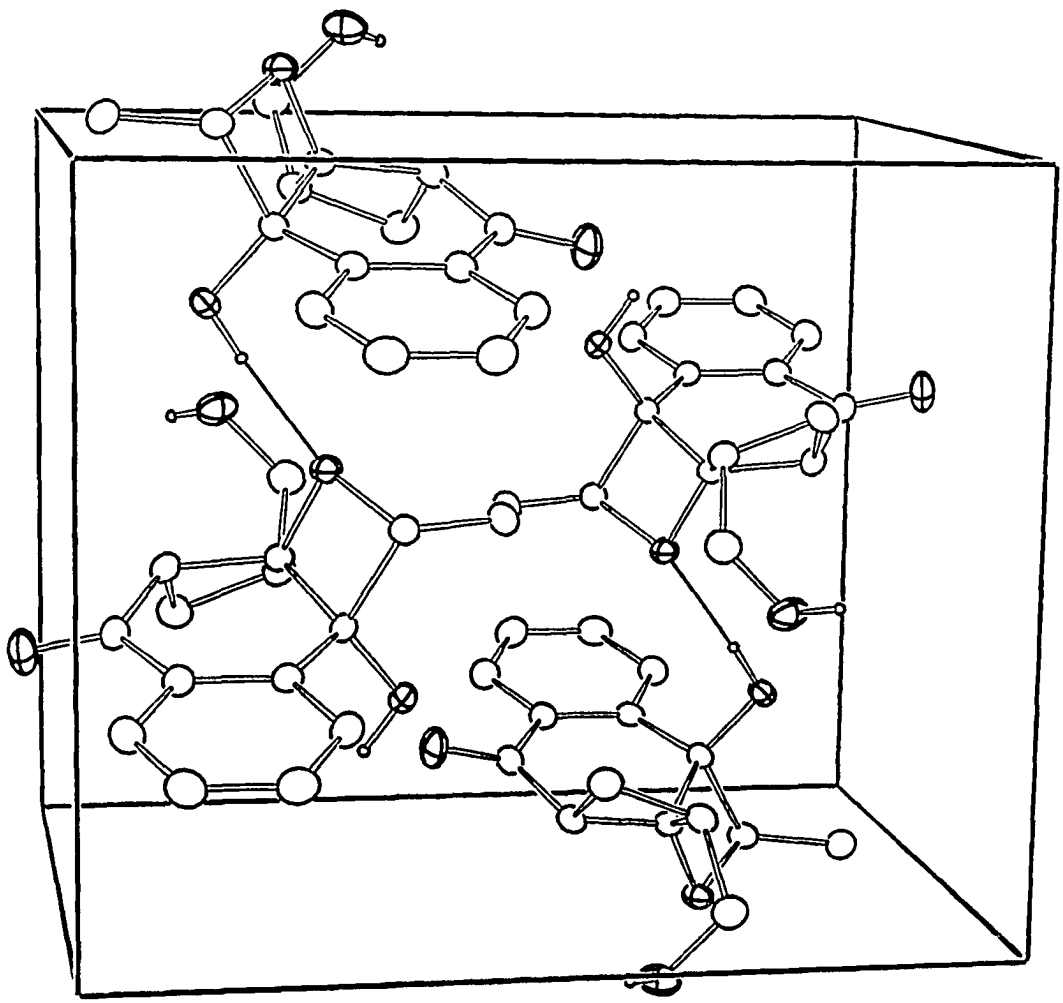
X-ray Crystal Structure of 75

Crystal Data

Formula	$C_{15}H_{16}O_4$
Formula weight	260.29
Space Group	$P2_1/c$
a, Å	9.610(2)
b, Å	12.625(1)
c, Å	10.646(2)
β, deg	90.940(9)
V, Å^3	1291.5(3)
Z	4
d_{calc}, g/cm^3	1.339
Crystal size, mm	0.62 × 0.44 × 0.40
μ(MoK$_\alpha$), cm^{-1}	0.904
Data collection instrument	Enraf-Nonius CAD4
Radiation (monochromated in incident beam)	MoK$_\alpha$(λ = 0.71073Å)
Orientation reflections, number, range (2θ)	25, 23.0 < 2θ < 33.8
Temperature, °C.	22(1)
Scan method	θ–2θ
Data col. range, 2θ, deg	4.0–50.0
No. unique data, total:	2263
with $F_o^2 > 3\sigma(F_o^2)$:	1688
Number of parameters refined	220
R[a]	0.0337
R_w[b]	0.0458
Quality-of-fit indicator[c]	1.50
Largest shift/esd, final cycle	0.01
Largest peak, e/Å^3	0.14(4)



Representation of the contents of the unit cell. Only the hydroxyl hydrogen atoms are shown, with some of the hydrogen bonding interactions indicated.



PART II.

SYNTHESIS OF DITERPENOID ALKALOIDS

INTRODUCTION

Until now, most bridgehead intermediate chemistry has relied on polar S_N1 substitution reactions. Less attention has been paid to the radical-mediated reaction. Since many polycyclic natural products have bridgehead carbon-carbon bonds, these radicals should have high utility in the synthesis of natural products.

This manuscript will detail a formal synthesis of modhephene by nucleophilic addition/ring contract methodology and a synthesis of the ABDE ring system of diterpene alkaloids by a bridgehead radical intermediate.

HISTORICAL

Radical chemistry dates back to 1900 when Gomberg investigated the formation and reactions of the triphenylmethyl radical.[1,2] Deeper insights into the formation , structure, and reaction of radicals were elucidated in 1950s and 1960s.[3] Recently, free radical reactions have achieved prominence in organic synthesis.[4] The mild reaction conditions and the normally high levels of chemo-,

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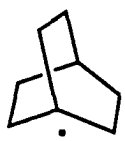

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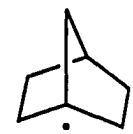

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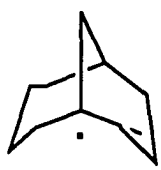

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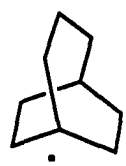

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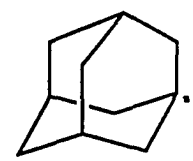

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regio-, and stereoselectivity allow radical reactions to serve as powerful tools in organic synthesis. However, bridgehead radicals have received much less attention compared with alkyl radicals.

Several bridgehead radicals have been generated by the reaction

conditions used for other alkyl radicals.

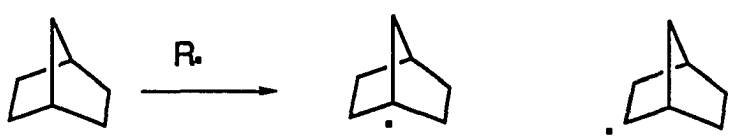
Hyperconjugation, through-space and through-bond interactions, nucleophilicity, nucleophilic sustitution and addition of bridgehead radicals have been investigated.

The relative strain energies of brigehead radicals have been investigated by molecular mechanics calculations and product analysis.[5]

Large long-range coupling in the ESR spectra of brigehead radicals were observed and described in terms of through-space and through-bond

Bu^tO•	100	0
Cl•	50	50

Bu^tO•	0	100
Br•	0	100
$(Me_3Si)_2N$•	29	71



Br•	0	100
$(Me_3Si)_2N$•	3	97

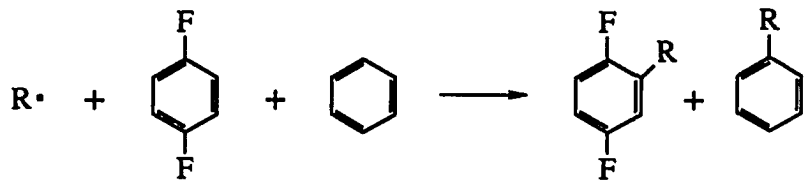
interactions.[6,7] Bridgehead radicals of bicyclo[1.1.1] pentane and bicyclo[2.1.1]hexane are more readily formed than that from bicyclo[2.2.1]heptane (norbornane). This fact was explained by these through-space and through-bond interactions.[8]

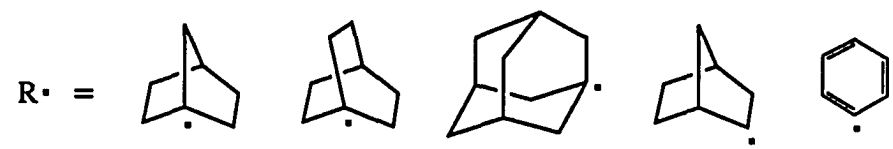
It has been established that electrophilicity increases in the series $sp^3 < sp^2 < sp$. Alkyl radicals are in fact nucleophilic and the nucleophilic properties are more pronounced when a radical is produced on a secondary rather than on a primary carbon atom.[9,10]

Tertiary radicals are difficult to investigate because of their tendency to undergo disproportionation rather than substitution reactions. Some studies on the alkylation of protonated heteroaromatic bases have shown, however, that tertiary radicals do effect aromatic substitution and are more nucleophilic than secondary radicals.[11]

The nucleophilic character of bridgehead radicals has been largely investigated, because a tertiary bridgehead radical would be expected to be of higher energy than an aliphatic tertiary radical, moreover, the rigidity of the system will block disproportionation.

When bridgehead free radicals were generated in an equimolar mixture of benzene and p-difluorobenzene by the thermal decomposition of the t-butylperoxyesters of 1-adamantyl, 1-bicyclo[2.2.2]octyl and 1-bicyclo[2.2.1]heptyl carboxylic acids, the reactivity of p-difluorobenzene relative to benzene indicated that bridgehead radicals possess nucleophilic character.[12]

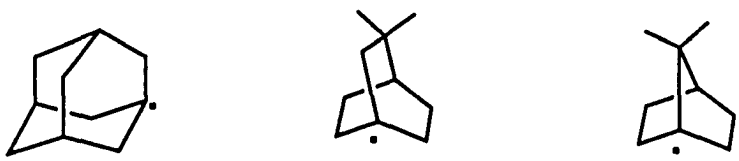




$C_6H_4F_2$ / C_6H_6	$K_{R\cdot}$	2.35	2.75	3.10	3.40	0.85

Further studies indicated that the nucleophilicity of bridgehead radicals varies as the ring system changes.[13]

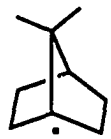
The reaction of the bridgehead radicals **9, 10** and **11** with protonated pyridines and quinones showed that the order of their nucleophilic properties is **9 > 10 > 11.**



9 **10** **11**

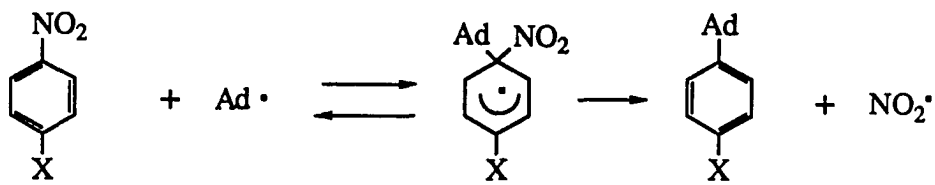
Alkyl radicals with an odd electron in a hybrid orbital with some s character can also be obtained at the bridgehead positions of polycyclic hydrocarbons. The relative rates of alkylation of 4-substituted pyridines by t-butyl and apocamphyl radicals were compared.[14]

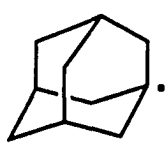
R ⟶ RX

X		
CN	1890	10.1
$COCH_3$	144	3.7
Cl	11.1	1.6
H	1	1
CH_3	0.15	0.26
OCH_3	0.0054	0.11

This great difference in selectivity of the two tertiary alkyi radicals must be ascribed to their different configuration. The unpaired electron occupies a p orbital in t-butyl and a sp^3 orbital in the apocamphyl. This difference affects the polarity, the polarizability of the radicals, the strength of the bonds formed, and, therefore, the nucleophilic character.[14]

Nucleophilic alkyl radicals react with nitroaromatic compounds to give substitution products in good yield. This is a synthetically useful example of a homolytic aromatic IPSO-Substitution reaction.[15]

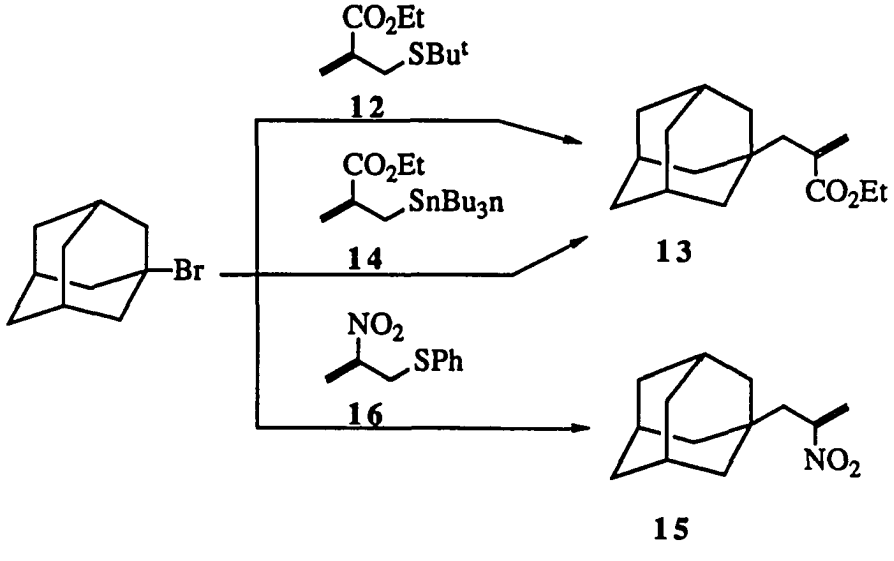


Ad• = 

At temperatures above 335 °K, the cubyl radical **2** reacts with greater selectivity than the adamantyl radical **9.** A study indicated that this unexpected order of selectivity is caused only by exceeding the isoselective temperature.[16]

Adamantane is an attractive substrate for the study of bridgehead intermediates. Although adamantane chemistry mainly focuses on its bridgehead cation reactions, a few examples of adamantyl bridgehead radical reaction have been observed.

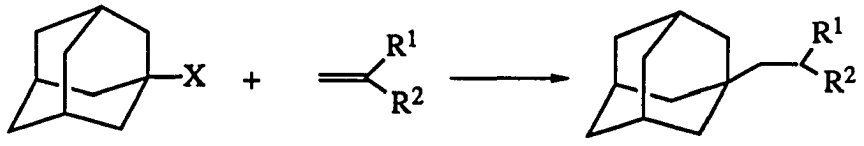
Introduction of a 2-substitued allyl group to the adamantane bridgehead by a radical-mediated reaction was studied.[17,18,19]



In comparison with **12** and **16**, reagent **14** required a significantly lower reaction temperature (80°C vs 132°C).

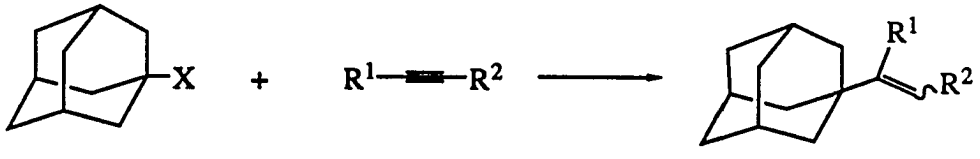
Introduction of β-functional alkyl and alkenyl groups to the adamantane bridgehead was carried out by radical-mediated reactions of 1-adamantyl bromide and iodide with alkenes and alkynes containing electron-withdrawing

groups in the presence of tri-n-butyltin hydride and AIBN or a zinc-copper ethanol/water system.[20,21]



X	R^1	R^2	Bu_3SnH, AIBN	Zn/Cu
Br	H	CN	80%	
Br	H	$COCH_3$	43%	
Br	H	CO_2CH_3	70%	
Br	CN	CO_2CH_3	0%	
I	CN	CO_2CH_3	36%	
Br	H	SOPh	35%	41%

Introducing alkenyl groups usually gives products in low yield.

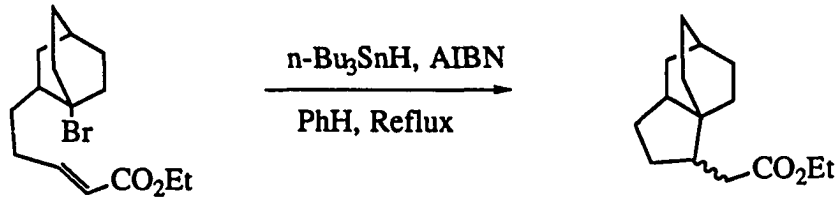


X	R^1	R^2	n-Bu_3SnH, AIBN	Zn/Cu
Br	H	CN	66%	

Br	H	CO_2CH_3	0%	
I	H	CO_2CH3	40%	
Br	H	$CO2CH_3$		33%
Br	H	Ph	0%	
I	H	Ph	15%	
Br	H	Ph		17%

The electron-withdrawing groups on the alkene and alkyne are necessary, because of the nucleophilicity of the adamantyl bridgehead radical.

An intramolecular reaction of a bridgehead radical was reported in 1985 from this laboratory.[22]

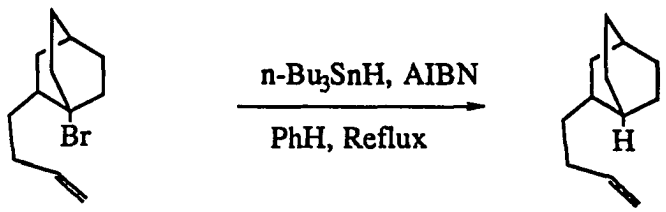


17 **18**

It is worthwhile noting that all the bridgehead radicals studied so far are nonfunctionalized. The bridgehead radical of **17** is the first example of a functionalized bridgehead radical.

They also found that[22] an activating group such as a carboethoxy group is essential for a successful radical cyclization.[23] Without an activated group, only

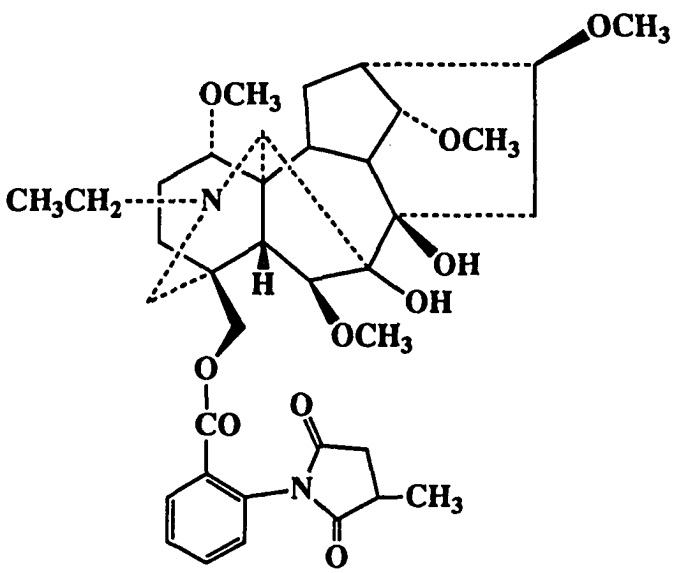
the reduction product was observed.



RESULTS AND DISCUSSION

Until now, most bridgehead intermediate chemistry has relied on polar S_N1 substitution reactions. Since the bridgehead cation is relatively stable and easily generated by a wide variety of methods, less attention has been paid to the radical-mediated reaction.

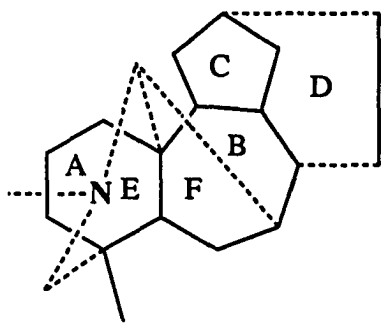
In order to study the application of bridgehead radical reactions in organic synthesis, we will focus on the synthesis of analogs of a polycyclic natural product. Since many polycyclic natural products have bridgehead carbon-carbon bond connections, these radicals should have high utility.

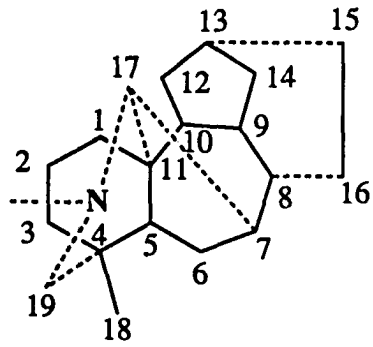


21

Among the polycyclic natural products there are many diterpene alkaloids isolated from the genera Aconitum, Delphinium, Anopterus, and Spiraea.[24] Most of them possess interesting biological activities.[25] For example,

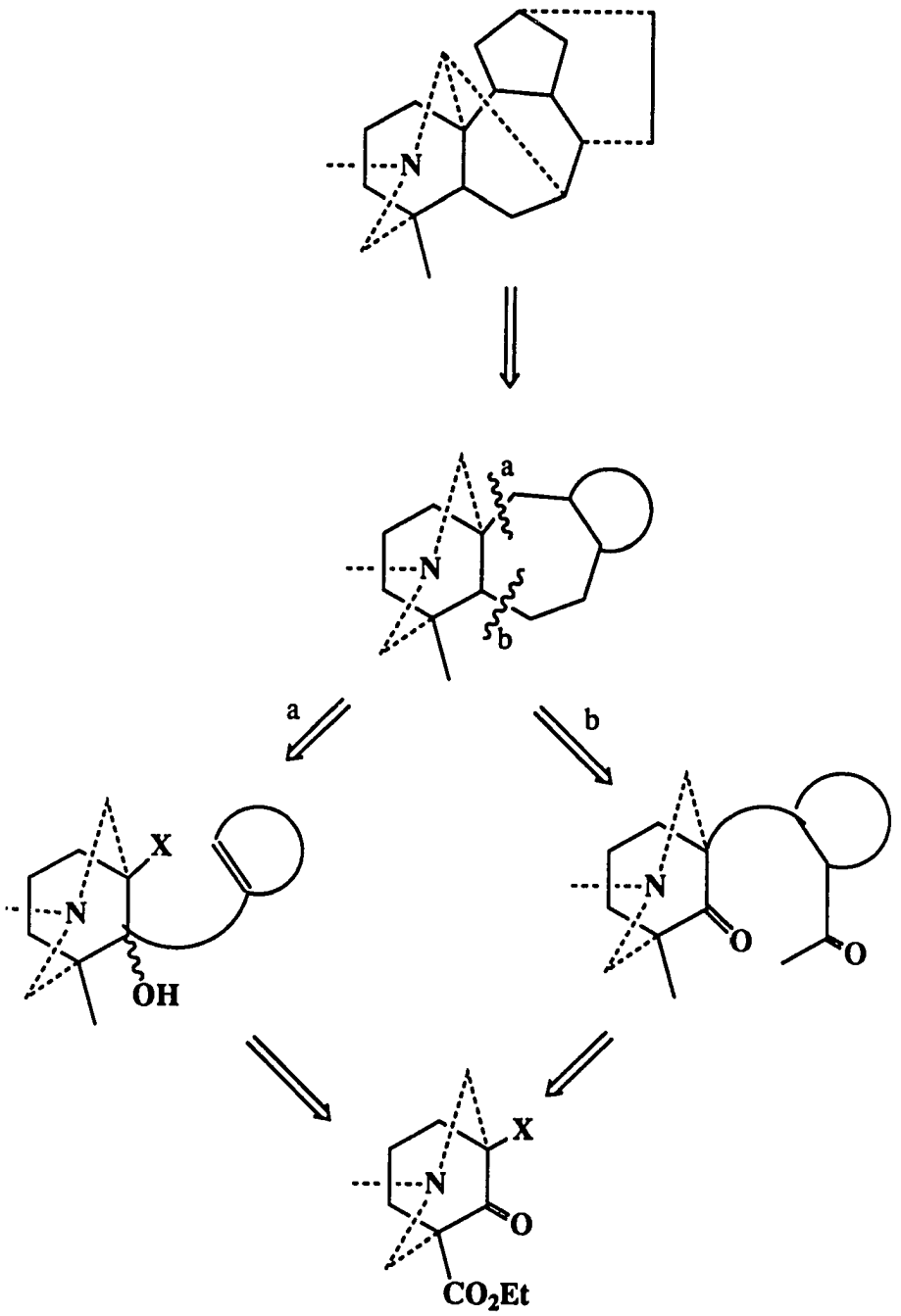
methyllycaconitine **21** is a Delphinium alkaloid which has been shown to be a potent inhibitor of a-bungarotoxin binding to housefly heads(K_{inh}=2.5x10^{10}M).[26] There are several features which are common to these diterpenoid alkaloids, the most obvious being the hexacyclic skeleton which is comprised of one seven-membered, three six-membered, and two five-membered rings. The lettering and numbering systems used for the aconitine-type and lycoctonine-type skeletons is shown below.





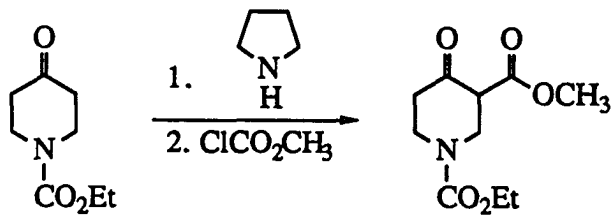
The synthesis of this complex structure is usually approached by a convergent pathway. Several researchers, most notable Wiesner,[27] Masamune,[28] Nagata et al.,[29] and Ihara et al.,[30] have reported clever syntheses of members of this class of compounds.

Our direct sythetic plan involved a disconnection leading to an AE ring system which would be converted into an advanced intermediate via bridgehead radical chemistry. Thus, the functionalized [3.3.1]nonane azabicyclo[3.3.1]nonane system **24** is a key intermediate in our approach.



24

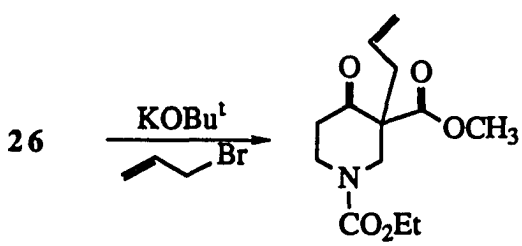
To achieve the synthesis of **24**, we started from commercially available piperidone **25**.



25 **26**

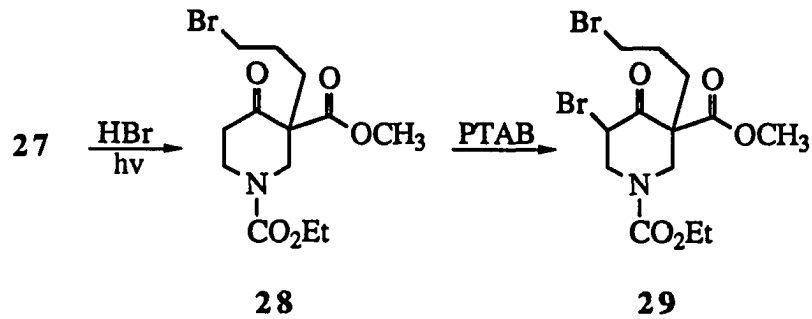
Piperidone **25** was activated as an enamine, followed by reaction with methyl chloroformate to give the ester **26** in 50% isolated yield with 45 % recovered starting material.

The b-keto ester **26** was treated with potassium t-butoxide and allyl bromide to give keto ester **27** in quantitative yield.



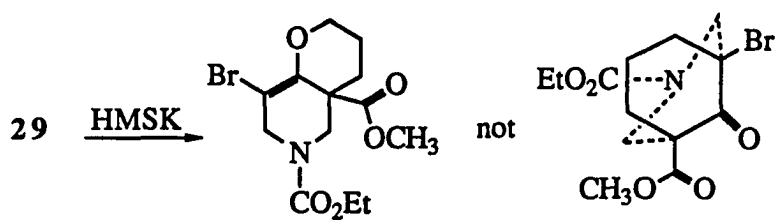
27

Regioselective addition of hydrogen bromide to the allyl group was performed by passing a stream of anhydrous HBr gas through a solution of **27** in pentane in the presence of a medium pressure Hg lamp.[31] Bromination of **28** by treatment of compound **28** with phenyltrimethylammonium perbromide (PTAB) in dichloromethane[32,33] gave dibromo ketoester **29.**



28 29

Unfortunately, treatment of **29** with potassium hexamethyldisilazide only gave intramolecular O-alkylation product **30**, instead of desired product **31**.

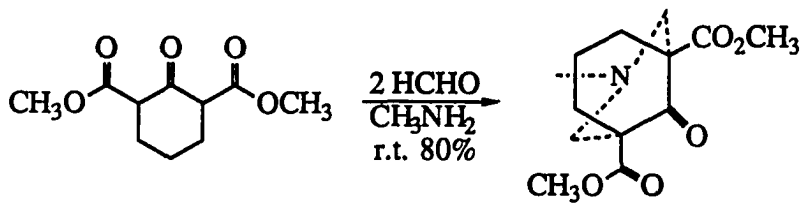


30 31

The compound **29** was treated with lithium hexamethyldisilazide to afford O-alkylation product also.

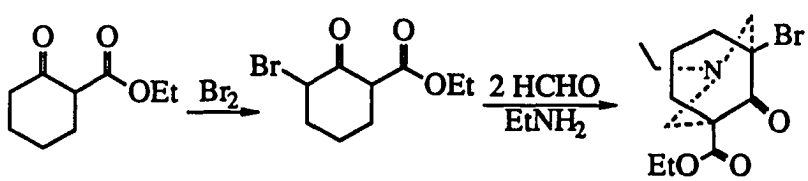
Since the synthesis of compound **31** from **25** did not work, we had to seek another synthetic route to key intermediate **24.**

Blicke and McCarty reported[34] that dimethylcyclohexanone-2,6-dicarboxylate reacted with formaldehyde and aqueous methylamine in methanol at room temperature to form dimethyl 3-methyl-3-azabicyclo[3.3.1]nonan-9-one-1,5-dicarboxylate in 80% yield.



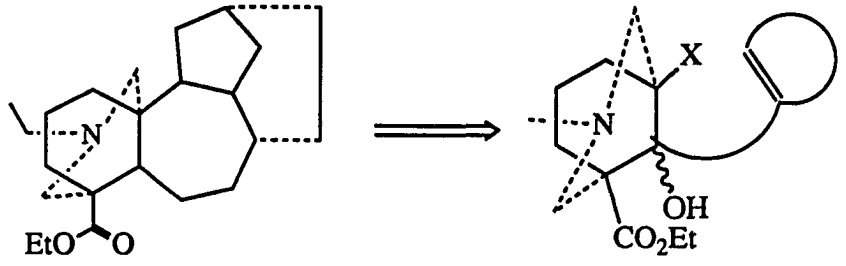
This would provide a direct route to our desired intermediate **24**, if bromoketo ester **33** were available.

In fact, **33** was prepared from readily available keto ester **32** in very good yield.[35,36] The most direct path from **33** to **34** was via a Mannich condensation with ethylamine and formaldehyde. Although displacement of the bromide by the amine seemed a likely complication, the double Mannich condensation actually proceeded very smoothly to generated **34** in 49% isolated yield with 40% recovered starting material.

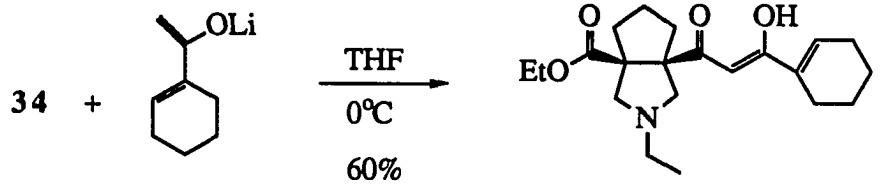


32 **33** **34**

The success of this important reaction has enabled us to apply our bridgehead radical methodology to the synthesis of diterpenoid alkaloids. Based on extensive literature precedent in the radical addition area, the intramolecular interception of the bridgehead radical appeared to offer the best chance for a high-yield connection of **34** with an alkene.[37]

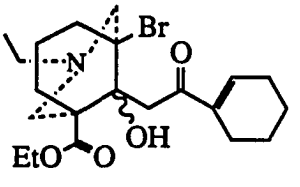


Towards this goal, bridgehead bromide **34** was added to a THF solution of the lithium enolate of 1-acetylcyclohexene at -78°C. The solution was then allowed to warm to 0°C. The expected product was the hydroxy ketone. Surprisingly, the only product isolated was the novel diketone **35**. The



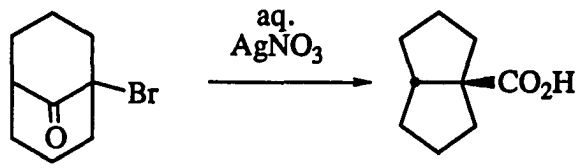
35

not

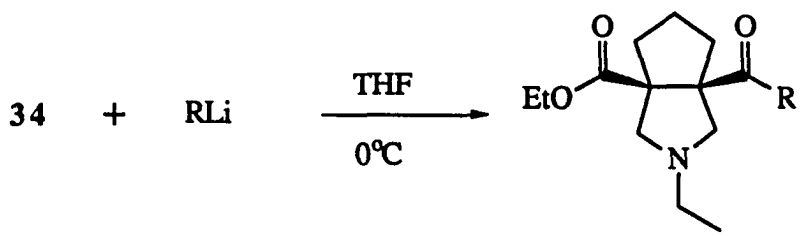


resonances at 92.986 and 180.126 (corresponding to the beta-diketone unit) in the CMR spectrum strongly supported the structural assignment. This product presumably arose from enolate addition to the ketone followed by ring contraction of the resulting tertiary alkoxide to a 3-azabicyclo[3.3.0]octane system. There is little precedent for this nucleophilic addition/ring contraction sequence in bridged ring systems. The rearrangement of the bromo ketone

shown below employed aqueous silver nitrate.[38]

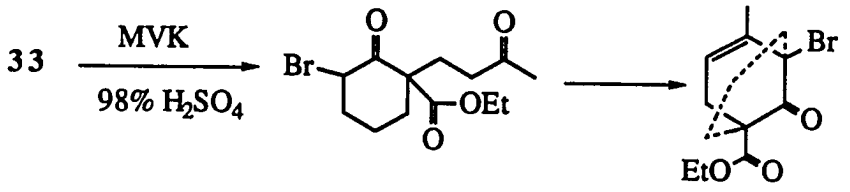


When **34** was treated with phenyl lithium, methyl lithium or the lithium enolate of acetophenone, rearrangement products were also observed.

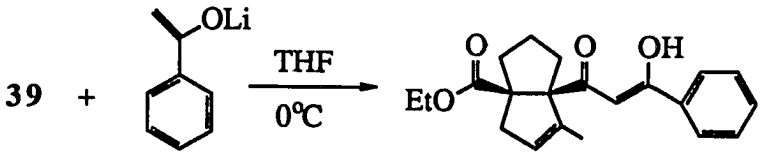


	R	% Yield
36	$PhCOCH_2$	58
37	Ph	73
38	Me	53

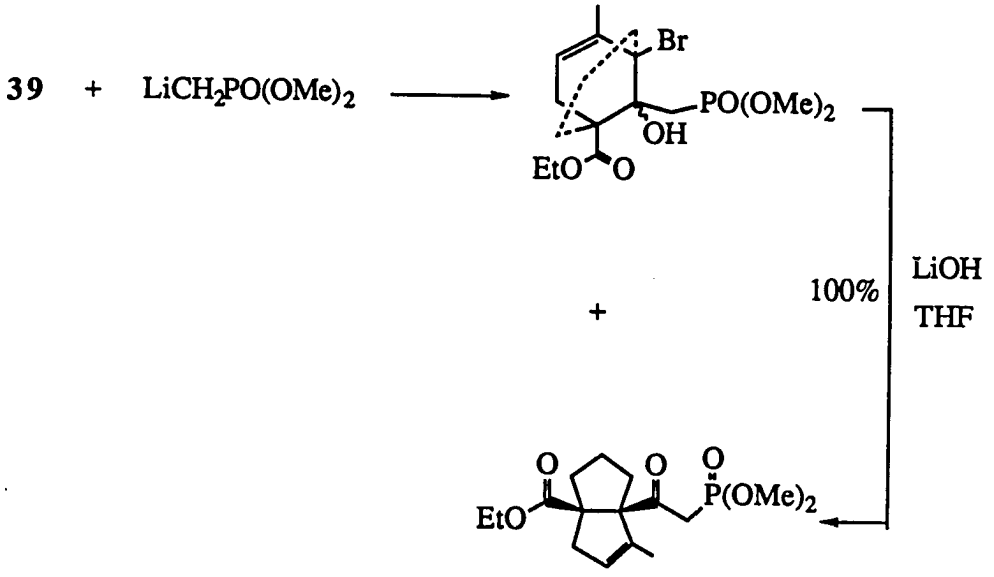
In order to determine whether the rearrangement would occur in the all-carbon framework, keto ester **39** was prepared. The reaction of bromoketone **33** and methyl vinyl ketone (MVK) in concentrated sulfuric acid at 0°C generated a diketone derived from a Michael addition reaction. This diketone could be cyclized to **39** in 77% yield by treatment with concentrated sulfuric acid at


33
MVK
98% H_2SO_4
Br
O
O
OEt
O
Br
O
EtO
O

39


39 +
OLi
THF
0°C
EtO
O
O
OH

40


39 + $LiCH_2PO(OMe)_2$
Br
$PO(OMe)_2$
OH
EtO
O
+
100%
LiOH
THF
EtO
O
O
$P(OMe)_2$

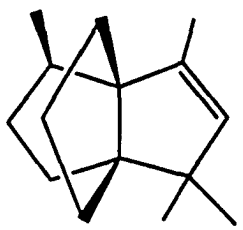
41

ambient temperature.[39] The reaction of **39** with the lithium enolate of acetophenone(-78°C to 0°C) furnished diketone **40** in 41% yield.

The reaction of **39** with $(MeO)_2POCH_2Li$ gave a mixture of rearranged and unrearranged products in 70% yield.

The unrearranged product can be completely converted to rearranged product **41** by treatment with LiOH in THF. The mechanism of nucleophilic addition/ring contraction that we proposed earlier was strongly supported by this conversion.

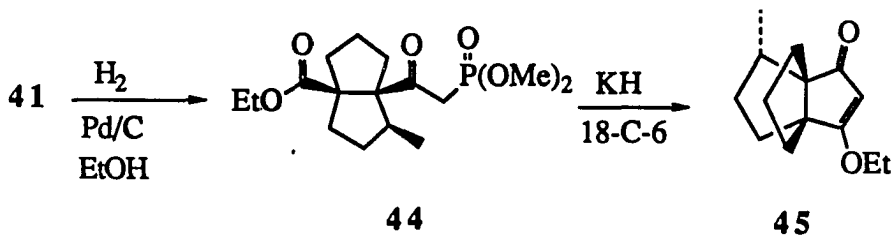
The bicyclic compound **41** contains two of the three rings of modhephene, **43**, a novel terpene.



43

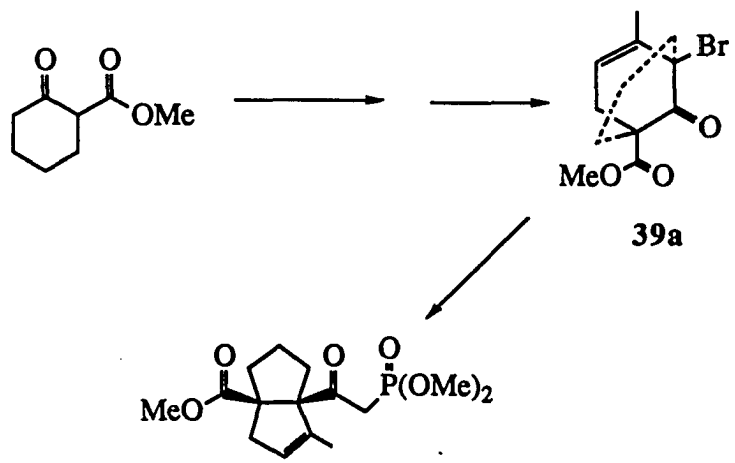
It is clear that this addition/ring contraction sequence could lead to a direct route to modhephene.

We expected catalytic hydrogenation of **41** should produce one isomer by reduction from the less hindered exo face. However, catalytic hydrogenation of **41** with 10% palladium on carbon in ethanol somehow gave completely exo isomer **44** in quantitative yield. Cyclization of **44** with potassium hydride and a catalytic amount of 18-crown-6 at 80°C in benzene afforded **45**.

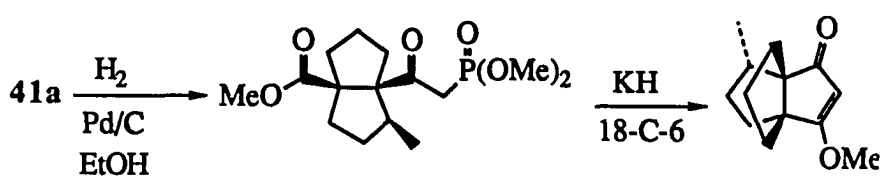


44 45

Methyl ester **41a** was also prepared by the same reaction sequence.

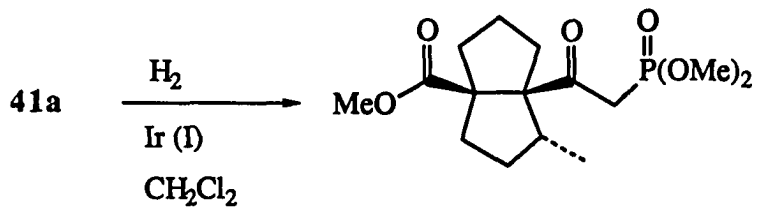


Hydrogenation of **41a** with palladium on carbon followed by an intramolecular Wittig cyclization gave the Mundy intermediate **45a**. This could be converted to epimodhephene in 2 steps.[40]

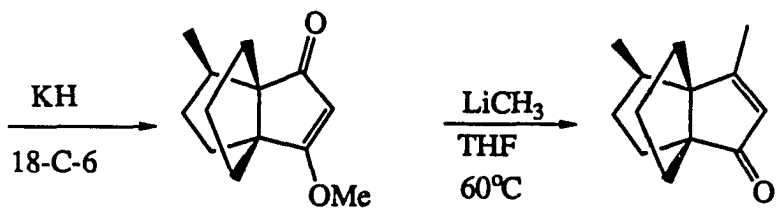


44a 45a

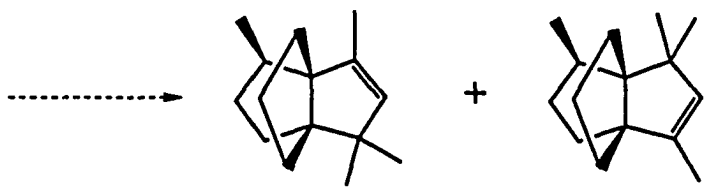
Hydrogenation of compound **41a** with Ir(I) in methylene chloride[41] gave the exo addition isomer **44b** in quantitative yield. Intramolecular Wittig cyclization of **44b**, followed by nucleophilic addition with methyllithium at 60°C in THF gave enone **46**, the intermediate in Curran's synthesis.[42] Compound **46** has been converted to modhephene and epimodhephene in one step.



44b



45b **46**



43

The comparison of Mundy's and Curran's intermediate with our intermediates **45b** and **46** is listed below.

M: 1.027 (d, 3 H, J = 6.6 Hz)

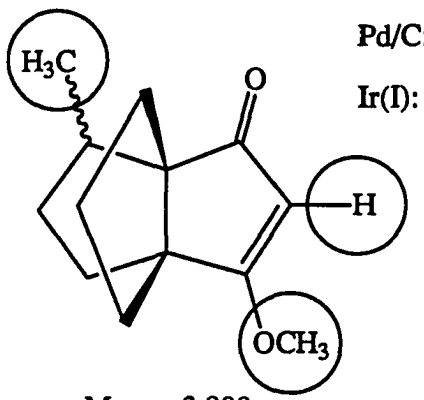
Pd/C: 1.032 (d, 3 H, J = 6.3 Hz)

Ir(I): 1.061 (d, 3H, J = 6.6 Hz)

M: 5.143

Pd/C: 5.150

Ir(I): 5.041



M: 3.808

Pd/C: 3.812

Ir(I): 3.815

C: 1.08 (d, 3 H, J = 6.6)

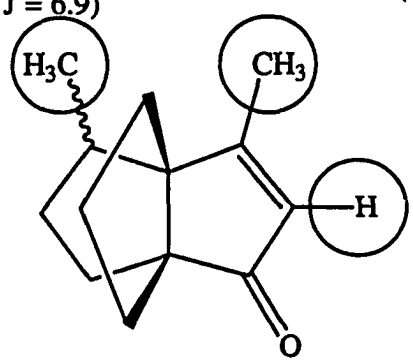
A: 1.084 (d, 3 H, J = 6.6)

M: 0.97 (d, 3 H, J = 6.9)

C: 2.05 (d, 3 H, J= 0.96)

A: 2.054 (d, 3 H, J = 1.2)

M: 2.08 (d, 3 H, J = 2.6)



C: 5.66

A: 5.666 (d, 1 H, J = 0.6

M: 5.81 (d, 1 H, J = 2.6

M: Mundy's intermediate

C: Curran's intermediate

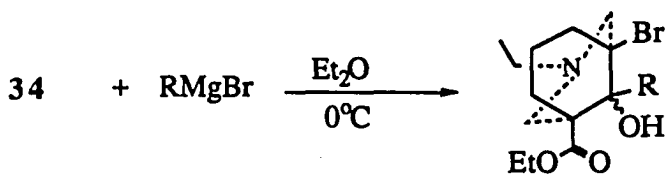
A: Author's intermediate

Pd/C: Intermediate was obtained by Pd/C catalytic hydrogenation.

Ir(I): Intermediate was obtained by Ir(I) catalytic hydrogenation.

The reaction of nucleophiles with bridgehead bromides **34** and **39** affords rearrangement products resulting from addition of the nucleophile to the carbonyl group followed by ring contraction. This rearrangement reaction is compatible with a variety of functional groups. The syntheses of an advanced intermediate in the Curran syntheses of modhephene confirmed the structural assignments of the rearrangement products. This discovery opened up a new pathway by which bicyclo[3.3.0]octanes and their 3-aza counterparts can be constructed.

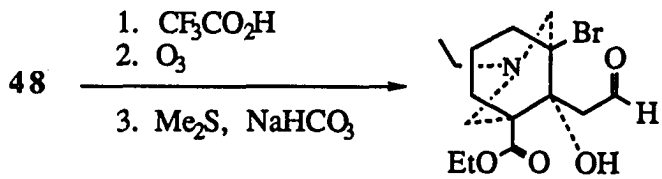
In our studies of the rearrangement reaction, we found that the reaction of **34** with methylmagnesium bromide or allylmagnesium bromide in ethyl ether at 0°C produced a tertiary alcohol as a mixture of stereoisomers in high yield. This result led us to continue to pursue intramolecular bridgehead radical reactions.



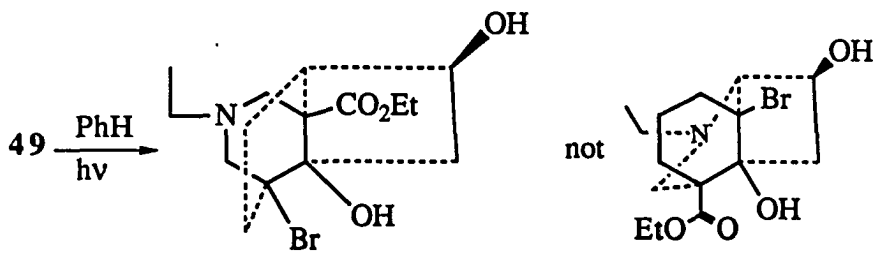
47 R = Me

48 R = $CH_2CH{=}CH_2$

After reaction of compound **48** with trifluoroacetic acid, followed by ozonolysis, hydroxy aldehyde **49** was obtained. Irradiation of **49** in benzene gave the type II photocyclization product, **50**, as a single isomer as evidenced by the proton NMR spectrum. However, X-ray crystal structure analysis of its hydrochloride salt showed the compound **50** is not our desired product. (see Appendix)



49

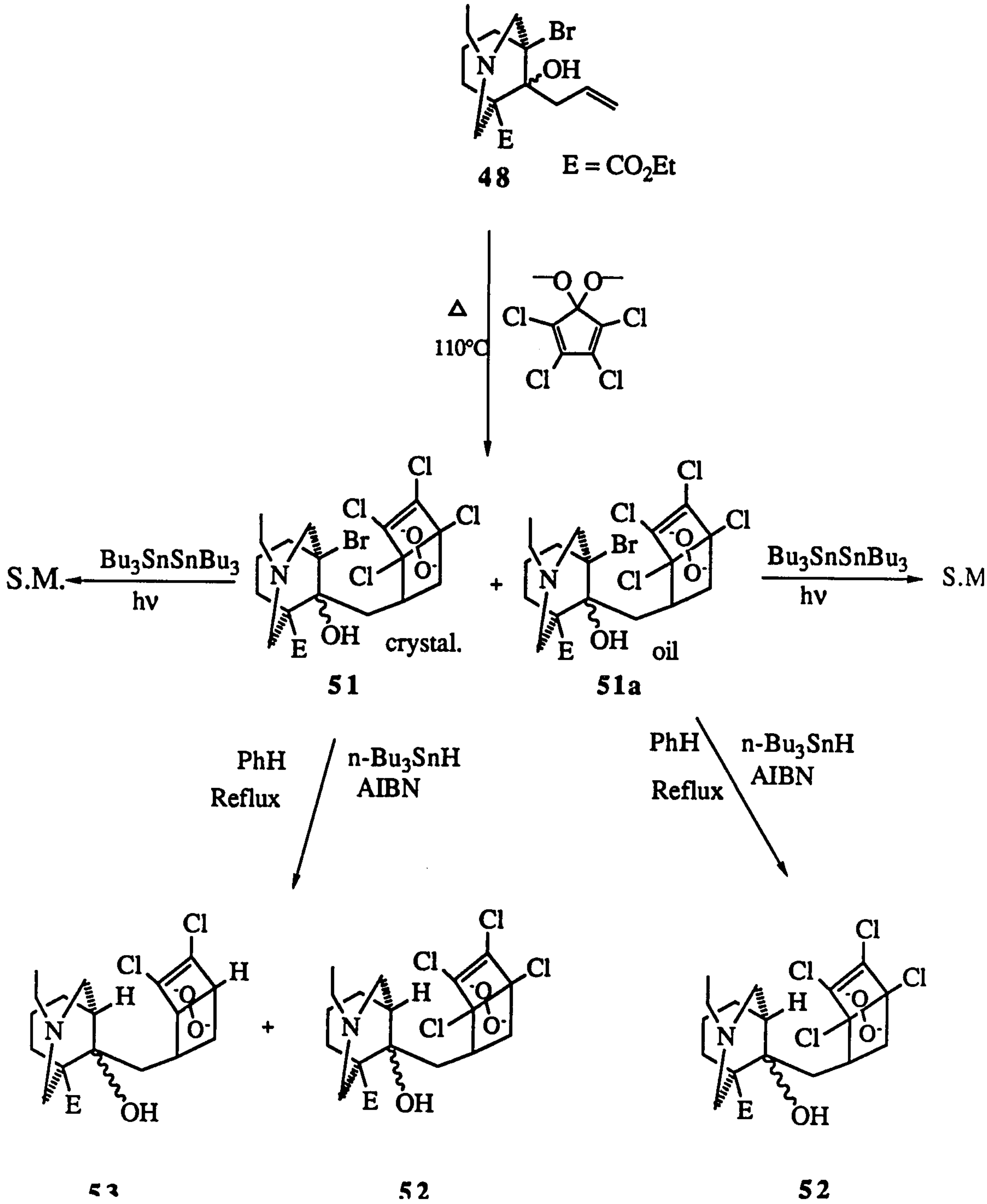


50

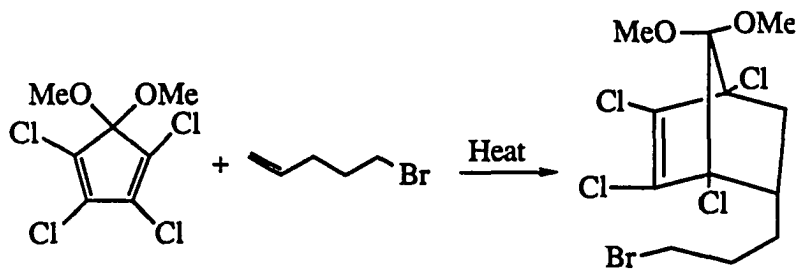
Jung and Hudspeth[43] have developed a method using the very highly reactive compound, 1,1-dimethoxytetrachlorocyclopentadiene as the diene component in a Diels-Alder reaction. The remarkable reactivity of this molecule in cycloaddition reactions was first recognized by McBee et al.,[44] who observed that even simple olefins such as allyl alcohol, allyl bromide and indene gave good yield of cycloadduct.

This very highly reactive diene reacted with **48** at 110°C to give the cycloaddition products as a diastereoisomeric mixture in very good yield.

However, when separated diastereoisomers **51** and **51a** were treated with 1.2 equivalents of n-Bu_3SnH and 15 mol% of AIBN in boiling benzene or toluene at various concentrations (0.1 M and 0.01 M) individually, the products obtained were **52** and **53**. Similar results were obtained using photochemistry.

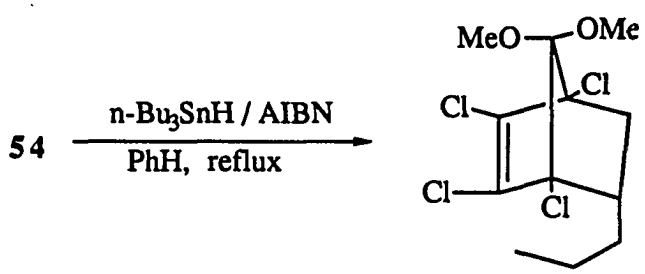

Br
OH
N
E
48
E = CO2Et
Δ
110°C
Cl
Cl
Cl
Cl
Bu3SnSnBu3
hν
S.M.
crystal.
51
+
oil
51a
S.M
PhH
Reflux
n-Bu3SnH
AIBN
H
53
52
52

The reason that ring closure did not occur is not clear. Diels-Alder cycloaddition of 1,1-disubstituted cyclopentadienes with olefins usually gives the endo isomer.H owever, we were not able to clarify the stereochemistry in our multifunctional system. To examine problem, we prepared **54** from 5-bromo-1-pentene. Since 1,1-dimethoxytetrachloro-pentadiene reacts with 5-bromopentene, it should give the endo isomer.



54

Treatment of **54** with n-Bu_3SnH under thermal conditions did not give a ring closure product.

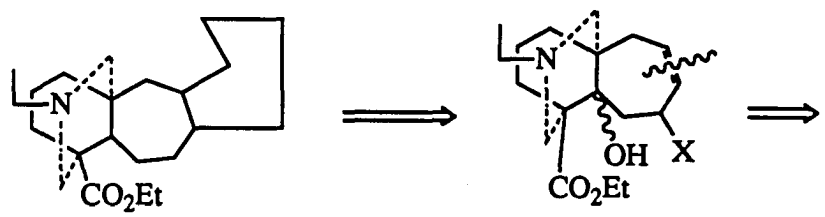


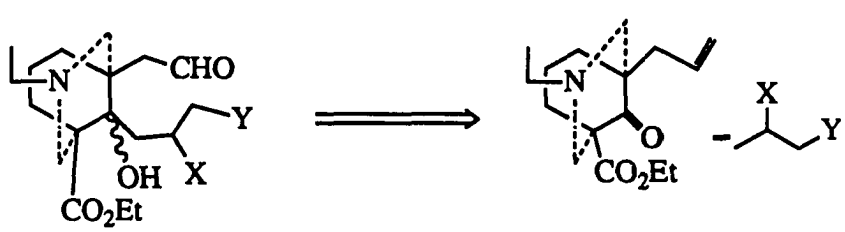
55

The failure of the ring closure reaction presumably is due to the fact that the hydrogen abstraction reaction is much faster than bridgehead radical addition.

The intramolecular bridgehead radical reaction did not give the desired ring closure product. Considerable attention was devoted to finding another pathway for B ring formation.

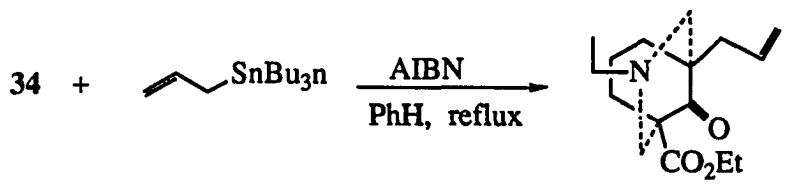
Since the double bond on the B ring is necessary for D ring formation, our synthesis plan involved B ring formation by an intramolecular aldol or Wittig reaction. Introduction of an allyl group on the bridgehead carbon by bridgehead radical carbon-carbon bond formation using allylstannanes[45] was possible. Only one example of allylation at a bridgehead carbon using an allylstannane reagent was reported.[19] This approach to carbon-carbon bond formation is very general with respect to tolerance of complex functionality. After a functional group was introduced by nucleophilic addition to the carbonyl group, ozonolysis and intramolecular aldol or Wittig condensation should proceed without difficulty.





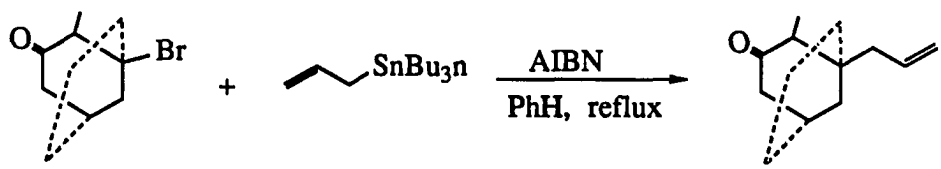
To test this approach, compound **34** was reacted with 2 equivalents of allyl

tri-n-butyltin in boiling benzene (0.1 M) containing 15 mol% of AIBN. The allylation product **56** was produced in 84% yield.

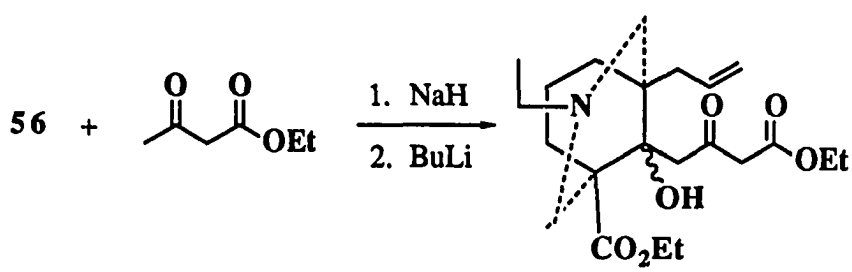


56

This is the first example of intermolecular bridgehead carbon-carbon bond formation by a multifunctionalized bridgehead radical intermediate. To test the generality of this bridgehead radical reaction, compound **57** was treated under the same reaction conditions. The allylation product **58** was also produced in good yield.



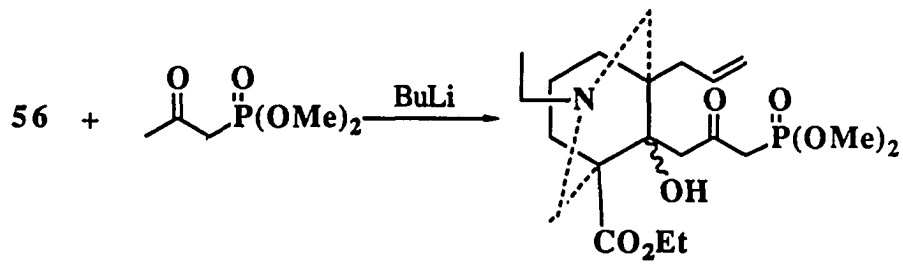
57 **58**



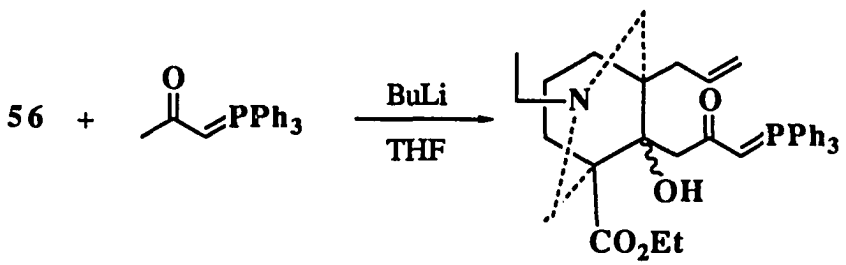
59

Reaction of **56** with suitable nucleophiles produced the tertiary alcohol as a mixture of stereoisomers in good yield.

However, ozonolysis of these tertiary alcohols after protection of the tertiary amine did not give the desired aldehydes.



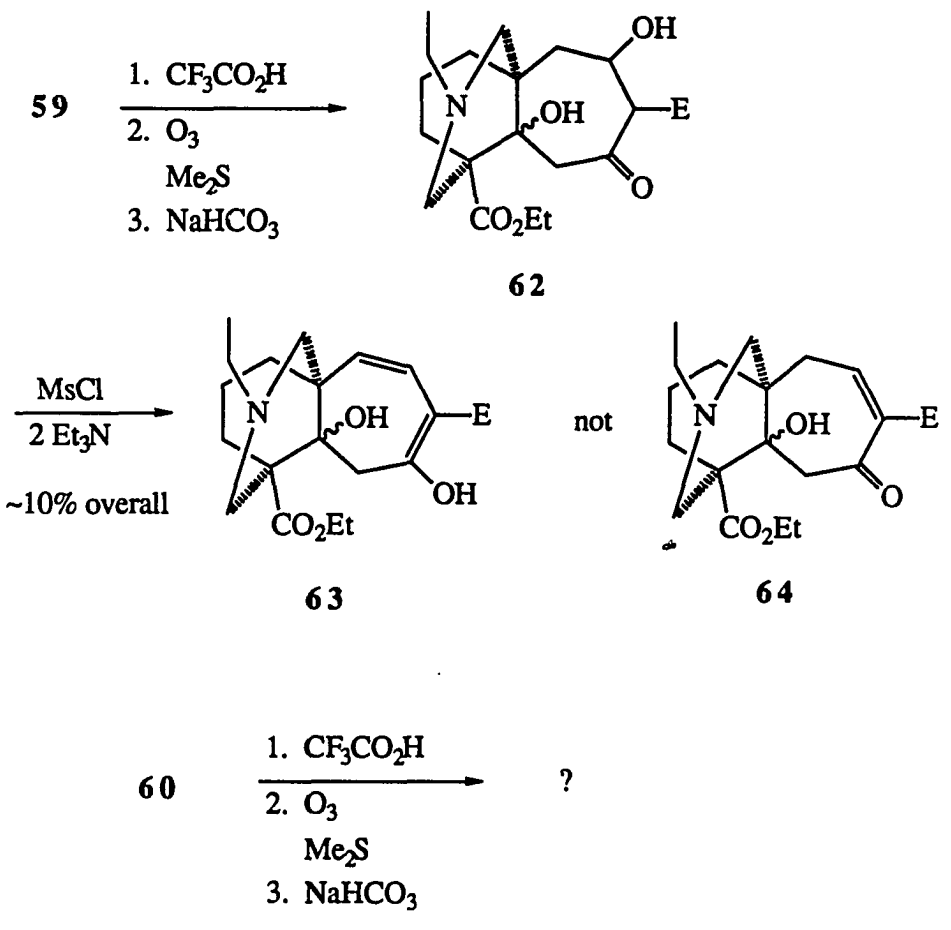
60



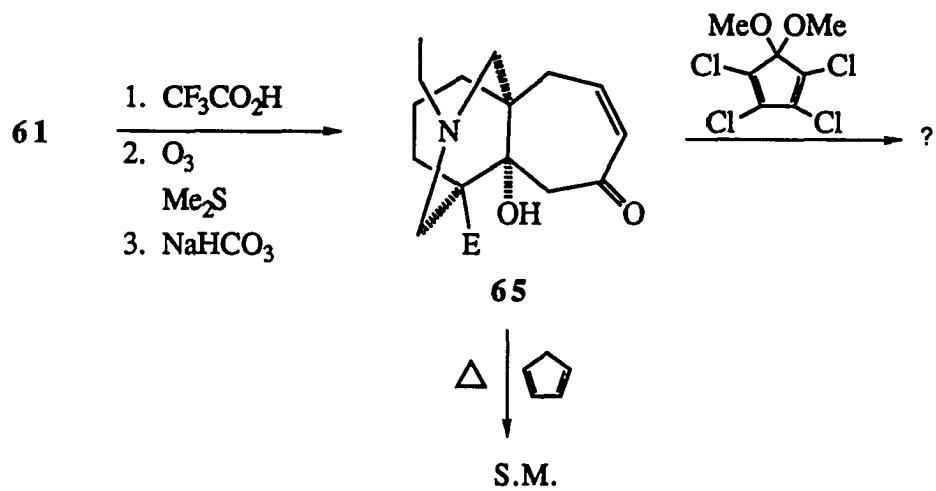
61

Compound **59** gave diol **62** in low yield. Diol **62** was treated with methanesulfonyl chloride and triethylamine giving enol **63**, instead of the desired diene **64**.

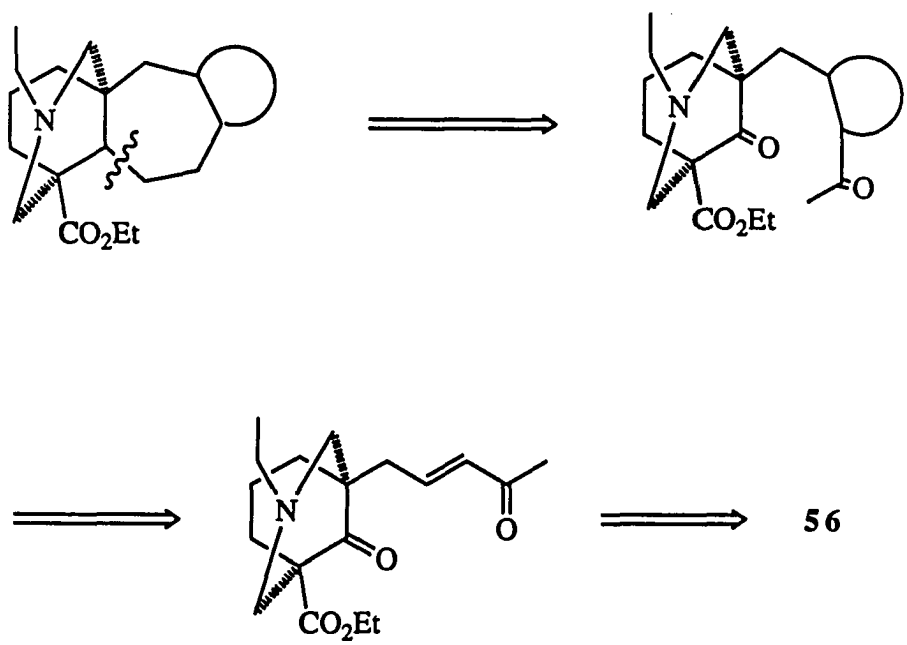
Ozonolysis of compound **60** gave unclear results under the same reaction conditions.



Ozonolysis of compound **61** under the same reaction conditions gave enone **65**. Unfortunately, this tricyclic a,b-unsaturated ketone **65** did not give a Diels-Alder cycloaddition product. The starting materials were recovered at relative low temperature and decomposition products were observed at higher temperature due to retro-aldol reaction.

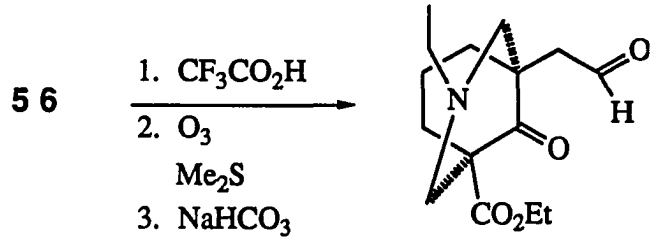


With this pathway closed, we decided to create the D ring first, followed by intramolecular aldol condensation to generate the B ring.



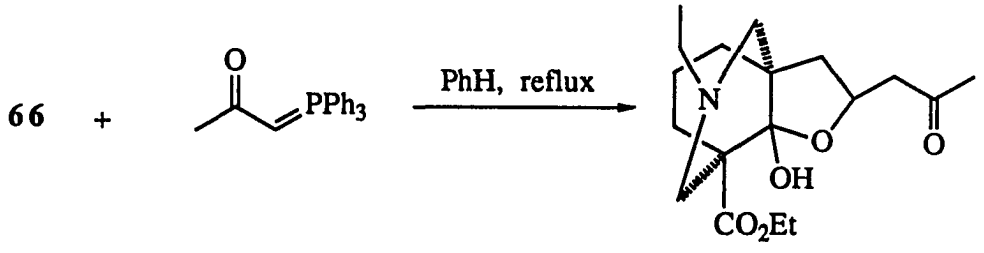
In the event, the direct ozonolysis of compound **56** provided the keto

aldehyde **66** in high yield.

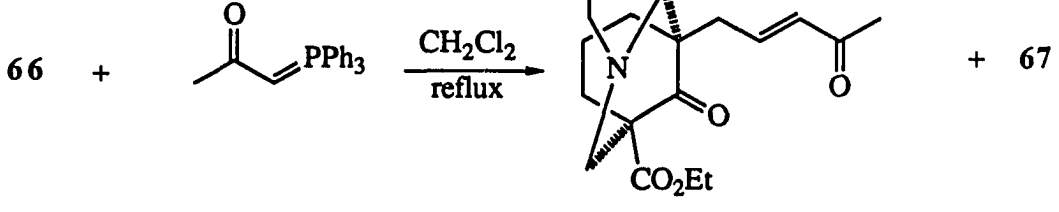


66

However, the reaction of compound **66** with 1-triphenylphosphoranylidene-2-propanone in boiling benzene did not give a clean Wittig reaction product. The hemiketal **67** was obtained.



67

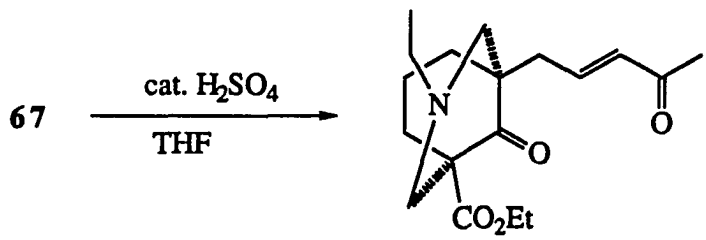


68

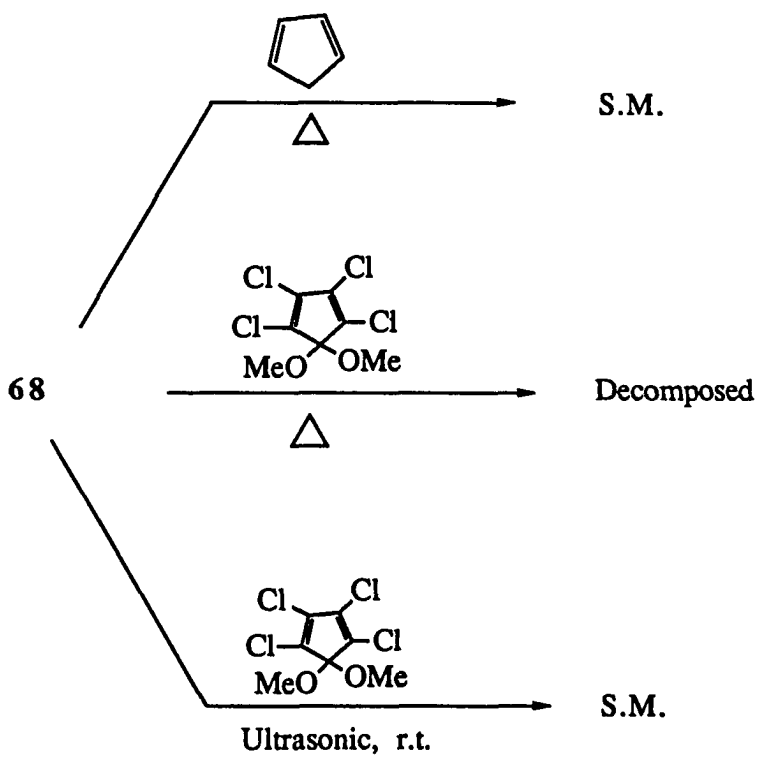
When the reaction was carried out in methylene chloride, a mixture of

compound **67** and Wittig reaction product **68** was produced. The ratio of **67** and **68** varied depending on the reaction time and temperature. It is impossible to separate these two compounds by flash chromatography, since they have exactly the same R_f on TLC.

Fortunately, we found that compound **67** could be easily converted to **68** in quantitative yield by stirring **67** in THF with a catalytic amount of sulfuric acid.

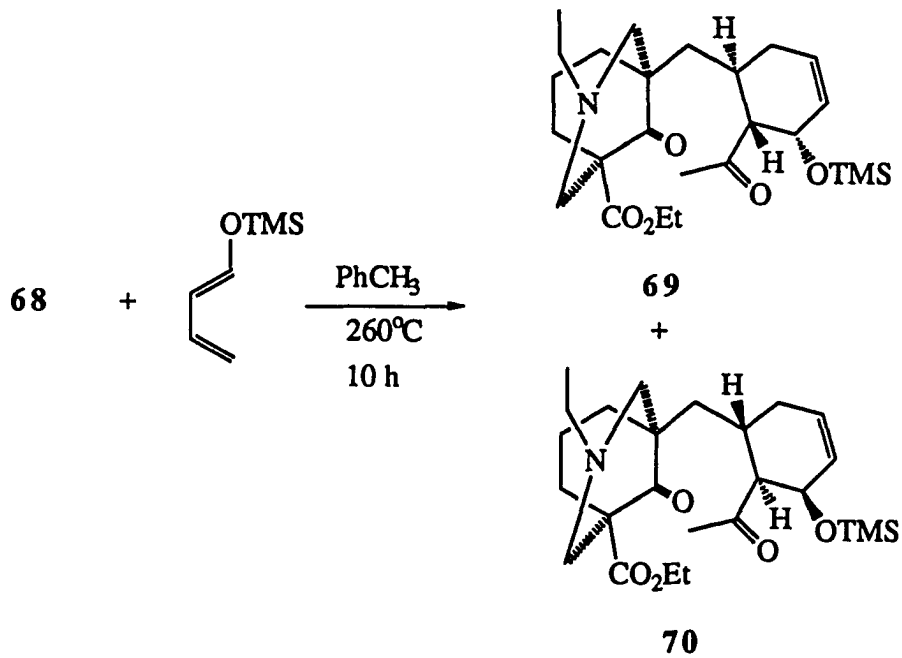


68

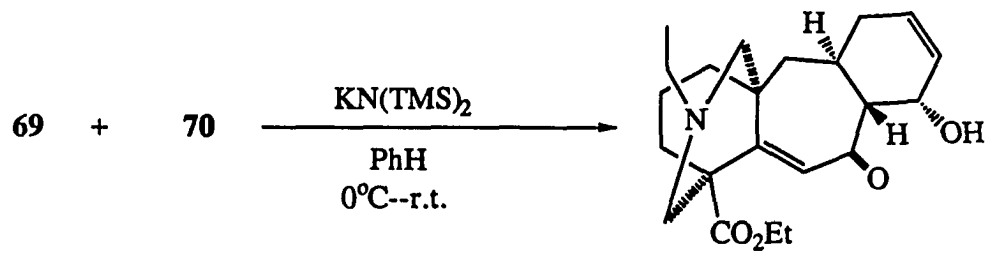


The Diels-Alder cycloaddition of **68** was investigated. The reaction of **68** with cyclopentadiene only gave recovered starting materials even at higher temperatures. The reaction with 1,1-dimethoxytetrachlorocyclopentadiene did not give the desired product either.

Eventually, the mixture of **68** and 1-trimethylsilyloxybutadiene in toluene was heated to 260°C for 10 hours. The Diels-Alder cycloaddition product was obtained as a diastereoisomeric mixture in good yield.



Treatment of the mixture with potassium hexamethyldisilazide in benzene from 0°C to room temperature afforded the intramolecular aldol cyclization product **71**. The compound **71** contains the ABDE rings of the hexacyclic skeleton of the lycoctonine-type diterpenoid alkaloids.



71

In summary, studies on the application of functionalized bridgehead radical intermediates in natural products synthesis led us to discover a new pathway to bicyclo[3.3.0]octanes and their 3-aza counterparts by nucleophilic addition/ring contraction of bridgehead bromides. The natural product modhephene was synthesized by use of this rearrangement methodology. A new, highly efficient bridgehead radical intermediate approach to the ABDE ring skeleton of lycoctonine-type diterpenoid alkaloids has been developed. The facile carbon-carbon bond formation at the bridgehead makes this process particularly attractive for the synthesis of polycyclic diterpenoid alkaloid systems.

EXPERIMENTAL

Unless otherwise noted, materials were obtained from commercial suppliers and were used without purification. THF and diethyl ether were distilled from sodium benzophenone ketyl under nitrogen prior to usage. Benzene was distilled from lithium aluminum hydride. Dichloromethane was distilled from calcium hydride. Unless otherwise noted, all reactions were conducted under an argon atmosphere and all organic extracts were dried over anhydrous magnesium sulfate. H:EA refers to hexanes:ethyl acetate solvent mixtures for TLC. The purity of all title compounds was determined to be >90% by proton NMR spectroscopy and/or elemental analysis. Melting points were determined on a Fisher-Johns melting point apparatus and are uncorrected. Infrared spectra were obtained on an IBM IR-90 Series FT IR spectrophotometer. High field (300 MHz) proton spectra were obtained with a Nicolet Magnetics Corporation NT-300 spectrometer. All chemical shifts are reported in δ relative to tetramethylsilane as an internal standard. Coupling constant (J) are reported in Hz. Abbreviations: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet. Carbon-13 NMR spectra were determined on a Nicolet NT-300 soectrometer and are reported in ppm relative to the central peak of $CDCl_3$ (77.06 ppm). High resolution mass spectra were recorded on a Kratos model MS-50 spectrometer. Low-resolution mass spectra were recorded on a Finnegan 4023 mass spectrometer. Silica gel used for flash chromatography was 230-400 mesh (Kieselgel 60) purchased from EM Science. Gravity column chromatography was performed on 60-200 mash silica gel purchased from Davison Chemical (WR Grace Inc.). Elemental analyses were performed by Galbraith Laboratories, Inc.

1-Ethyl-3-methyl-3-allyl-4-piperidone-1,3-dicarboxylate **27**

To a solution of keto ester **26** (4.0 g, 17.5 mmol) in 30 mL of DMF was added potassium t-butoxide (2.35 g, 20.96 mmol). The mixture was stirred for 10 min followed by the dropwise addition of allyl bromide (3.1 g, 26.25 mmol). The reaction was stirred overnight at room temperature, then 50 mL of water was added. The resulting mixture was extracted with methylene chloride and then washed with water and brine. The crude product was dried, filtered, concentrated, and purified by chromatography on silica gel using 3:1 hexanes:ethyl acetate to afford 4.0 g (85.0% yield) of **27**. HRMS calcd for $C_{13}H_{19}O_5N$: 269.12633, found: 269.12595. ^1H NMR ($CDCl_3$): 1.294 (t, 3 H, J = 7.2 Hz), 2.412-2.762 (m, 4 H), 3.215 (d, 2 H, J = 13.8 Hz), 3.369 (m, 1 H), 3.717 (s, 1 H), 4.187 (q, 2 H, J = 7.2 Hz), 4.526 (d, 1 H, J = 13.2 Hz), 5.116 (m, 2 H), 5.755 (m, 1 H). MS: 269, 240, 228, 210, 196, 168, 95. CMR ($CDCl_3$) 203.890, 170.161, 155.100, 132.068, 119.278, 61.872, 60.951, 52.489, 49.759, 43.383, 39.683, 36.118, 14.554. IR (neat) 3080, 2982, 2955, 1705, 1433, 1387, 1234, 1134, 1013, 926, 768 cm^{-1}. TLC (3:1 = H:EA) R_f = 0.28.

1-Ethyl-3-methyl-3-(3-bromopropyl)-4-piperidone-1,3-dicarboxylate **28**

A solution of unsaturated ketone **27** (4.15 g, 15.43 mmol) in 500 mL of pentane was placed in a quartz photochemical reaction vessel and flushed with N_2. Then gaseous HBr was passed through the solution for 1 h while the solution was irradiated with the light from a medium-pressure Hg lamp. The resulting pentane solution was flushed with N_2 to remove most of the HBr and was washed repeatedly with saturated aqueous $Na_2S_2O_3$. The resulting organic solution was dried and concentrated in vacuo to provide 3.67 g (68.0%

yield) of bromoketone **28**. HRMS Calcd for $C_{13}H_{20}O_5NBr$: 349.05249, found 349.05221. ^1H NMR ($CDCl_3$): 1.30 (t, 3 H, J = 7.2 Hz), 1.761-1.968 (m, 4 H), 2.50 (m, 1 H), 2.716 (m, 1 H), 3.266 (d, 1 H, J = 13.8 Hz), 3.390 (dd, 2 H, J = 6.0, 5.4 Hz), 3.448 (m, 1 H), 3.745 (s, 3 H) 4.107 (m, 1 H), 4.194 (q, 2 H, J = 7.2 Hz), 4.459 (dd, 1 H, J = 13.8, 1.8 Hz). MS: m/e 351, 349, 322, 320, 306, 304, 292, 290, 278, 276. CMR ($CDCl_3$) 204.149, 170.307, 154.996, 61.946, 60.780, 52.536, 50.167, 43.506, 36.498, 33.131, 30.403, 27.857, 14.555. TLC (2:1 H:EA) R_f = 0.42.

1-Methyl-3-ethyl 5-bromo-6,3-oxazabicyclo[4.4.0]dec-5-ene-1,3-dicarboxylate **30**

To a solution of dibromoketone **29** (4.16 g, 9.72 mmol) in 60 mL of THF at -78 °C was added potassium hexamethyldisiliazide solution (2.086 g, 10.5 mmol). The reaction solution was stirred at -78 °C for 2 hours and then slowly warmed to room temperature for another 2 hours. The reaction solution was poured into 50 mL of 0.1 N HCl. The product was extracted with methylene chloride, and washed with water and brine. The organic layer was dried, filtered, concentrated, and purified by chromatography on silica gel using 3:1 hexanes : ethyl acetate to provide 2.63 g (78% yield) of diester. HRMS calcd for $C_{13}H_{18}O_5NBr$: 347.03684, found 347.03749. ^1H NMR ($CDCl_3$): 1.254 (t, 3 H, J = 7.2 Hz), 1.385 (m, 1 H), 1.837 (m, 1 H), 2.392 (m, 1 H), 2.915 (m, 1 H), 3.651 (dd, 1 H, J = 11.1, 1.8 Hz), 3.700 (s, 3 H), 3.864 (m, 1 H), 4.127 (q, 2 H, J = 7.2 Hz), 4.206 (m, 2 H), 4.320-4.722 (m, 2 H). IR (neat) 2986, 2951, 1728, 1697, 1475, 1456, 1250, 1175, 1016, 810 cm^{-1}. MS: m/e 349, 347, 320, 318, 290, 288, 276, 274, 268, 260, 167. CMR ($CDCl_3$) 172.327, 154.568, 147.285,

69.357, 61.766, 52.187, 50.768, 50.482, 48.909, 48.469, 29.264, 22.531, 14.514. TLC (3:1 H:EA).

Ethyl 3-ethyl-5-bromo-9-oxo-3-azabicyclo[3.3.1]nonane carboxylate **34**

To a solution of ethyl 3-bromo-2-oxocyclohexane carboxylate (4.98 g, 20 mmol) in 120 mL of MeOH at 25°C was added formaldehyde (37% in H_2O, 3.24 g, 40 mmol) and ethylamine (70% in H_2O, 1.29 g, 20 mmol). The solution was stirred at 25°C for 48 h. The methanol was removed in vacuo and the product was taken up in CH_2Cl_2. The solvent was removed in vacuo. The residue was purified by chromatography On silica gel using 15:1 H:EA to afford 3.12 g (49% yield) of ester **34**. The starting ester (1.1 g) was also recovered. The product was a colorless oil with R_f = 0.28 in 15:1 H:EA. ^1H NMR ($CDCl_3$): 4.232 (q, J = 7.2, 2 H), 3.602 (dd, J = 2.4, 10.8 Hz, 1 H), 3.253 (dd, J = 2.4, 11.4 Hz, 1 H), 3.144 (m, 2 H), 3.033 (dd, J = 2.1, 11.7 Hz, 1 H), 2.952 (dd, J = 2.1, 11.1 Hz, 1 H), 2.700 (m, 1 H), 2.570 (m, 1 H), 2.448 (q, J = 7.2, 2 H), 2.560 (m, 1 H), 1.600 (m, 1 H), 1.299 (t, J = 7.2 Hz, 3 H), 1.117 (t, J = 7.2, 3 H); IR (Det.) 2976, 2935, 2814, 1730, 1454, 1258, 700 cm^{-1}; MS: m/e 319, 317, 302, 300, 274, 272, 238, 220, 192, 164, 125, 108; HRMS: m/e for $C_{13}H_{20}O_3NBr$ calcd. 317.06266, measured 317.06197; CMR ($CDCl_3$) d 201.984, 169.704, 69.738, 68.697, 61.428, 61.097, 59.835, 50.450, 46.278, 36.270, 22.783, 14.032, 12.488.

General Procedure for the Nucleophilic Addition/Ring Contraction Reaction

To a solution of ketone **34** (1.0 equiv.) in THF (0.1 M) at -78°C was added the anion (1.1 equiv.). The solution was stirred at -78°C for 10 min and then allowed to slowly warm to 0°C over 1 h. Acetic acid in THF was added at 0°C to

quench the reaction. Water was added and the aqueous layer was then extracted twice with ether. The combined organic layers were dried and concentrated in vacuo. The residue was purified by chromatography on silica gel with H:EA.

35: NMR ($CDCl_3$): 15.489 (s, 1 H), 6.862 (s, 1 H), 5.866 (s, 1 H), 3.972 (m, 2 H), 3.154 (d, J = 9.0 Hz, 1 H), 2.854 (d, J = 9.0 Hz, 1 H), 2.627 (dd, J = 9.0, 2.1 Hz, 2 H), 2.485 (m, 2 H), 2.223 (m, 6 H), 1.843 (m, 4 H), 1.630 (m, 4 H), 1.116 (t, J = 6.6 Hz , 3 H), 1.091 (t, J = 6.6 Hz, 3 H); IR (net) 3383, 2935, 2802, 1730, 1641, 1585, 1448, 1277, 1209, 1040 cm^{-1}; MS: m/e 361, 344, 316, 288, 270, 252, 209, 194, 164, 136, 127, 109, 91, 71, 58; HRMS: m/e for $C_{21}H_{31}O_4N$ calcd. 361.22531, measured 361.22518; CMR ($CDCl_3$): 201.343, 180.126, 175.003, 135.525, 132.955, 92.986, 66.388, 65.114, 64.351, 63.112, 60.423, 49.343, 39.070, 39.155, 25.822, 25.284, 23.450, 22.019, 21.476, 13.631; TLC (1:1 H:EA) R_f = 0.60.

36: NMR (CCl_3D) : 16.002 (s, 1 H), 7.938 (d, J = 7.2 Hz, 2 H), 7.450 (m, 3 H), 6.404 (s, 1 H), 3.960 (m, 2 H), 3.238 (d, J = 9.3 Hz, 1 H), 2.937 (d, J = 9.0 Hz, 1 H), 2.647 (t, J = 9.6 Hz, 2 H), 2.536-2.223 (m, 4 H), 1.882 (m, 4 H), 1.113 (t, J = 6.6 Hz, 3 H), 1.092 (t, J = 6.6 Hz, 3 H); IR (net) 2968, 2874, 2804, 1730, 1610, 1574, 1454, 1279, 768, 694 cm^{-1}; MS: m/e 357, 340, 312, 284, 252, 210, 164, 136, 105, 71, 58; HRMS: m/e for $C_{21}H_{27}O_4N$ calcd. 357.19401, measured 357.19454; CMR (CCl_3D): 201.348, 180.528, 175.128, 134.616, 131.955, 128.552, 126.743, 94.178, 66.382, 65.255, 64.380, 63.496, 60.694, 49.466, 39.207, 37.060, 25.396, 13.768, 13.728; TLC (1:1 H:EA) R_f = 0.38.

37: NMR ($CDCl_3$): 7.708 (m, 2 H), 7.432 (m, 3 H), 4.069 (q, J = 7.2 Hz, 2 H), 3.173 (d, J = 9.0 Hz, 1 H), 2.900 (s, 2 H), 2.823 (d, J = 9.3 Hz, 1 H), 2.472 (m, 2 H), 2.318 (m, 2 H), 2.171 (m, 1 H), 1.936 (m, 3 H), 1.192 (t, J = 7.2 Hz, 3 H), 1.075 (t, J = 7.2 Hz, 3 H); IR (neat) 2970, 2874, 2806, 1732, 1678, 1600, 1447, 1271, 717, 698 cm^{-1}; MS: m/e 315, 298, 272, 242, 226, 210, 188, 156, 136, 105, 77, 71, 58; HRMS: m/e for $C_{19}H_{25}O_3N$ calcd. 315.18344, measured 315.18377; CMR ($CDCl_3$): 203.850, 175.646, 137.583, 131.635, 127.987, 127.863, 68.788, 65.321, 63.847, 62.947, 60.143, 49.535, 40.095, 38.173, 25.577, 13.919, 13.551; TLC (1:1 H:EA) R_f = 0.38.

38: NMR ($CDCl_3$): 4.075 (q, J = 7.2 Hz, 2 H), 3.025 (d, J = 9.3 Hz, 1 H), 2.790 (d, J = 9.0 Hz, 1 H), 2.663 (d, J = 8.4 Hz, 2 H), 2.450 (m, 2 H), 2.236-2.167 (m, 2 H), 2.134 (d, J = 0.6 Hz, 3 H), 1.821 (m, 4 H), 1.212 (t, J = 6.9 Hz, 3 H), 1.079 (t, J = 7.5 Hz, 3 H); IR (neat) 2968, 2874, 2804, 1730, 1705, 1448, 1229, 1028, 932 cm^{-1}; MS: m/e 253, 236, 210, 180, 164, 136, 123, 108, 80, 71, 58; HRMS: m/e for $C_{14}H_{23}O_3N$ calcd. 253.16779, measured 253.16716; CMR ($CDCl_3$): 209.029, 175.305, 69.483, 64.438, 64.003, 62.405, 60.564, 49.387, 39.036, 37.328, 27.267, 25.163, 13.813, 13.548; TLC (1:1 H:EA) R_f = 0.26.

Methyl 5-Bromo-4-methyl-9-oxo-bicyclo[3.3.1]nonane carboxylate **39a**

Methyl 2-cyclohexanonecarboxylate (4.70 g, 20 mmol) and methyl vinyl ketone (2.1 g, 30 mmol) were cooled to -78°C. To this swirled mixture was added slowly dropwise 98% H_2SO_4 (5 mL). The stirred mixture was allowed to slowly warm to 0°C. The mixture was then stirred at 25°C for 36 h. The mixture was carefuly poured into 200 mL of cold satd. $NaHCO_3$. The aqueous layer was

extracted with ether three times. The combined organic layers were dried and concentrated in vacuo. The residue was purified by chromatography on silica gel using 10:1 H:EA to afford 1.98 g (35% yield) of ester **39a**. This clear liquid had an R_f of 0.38 in 5:1 H:EA. ^{1}NMR ($CDCl_3$): 5.748 (1 H, m), 3.784 (3 H, s), 3.350 (1 H, m), 2.619-2.262 (4 H, m), 2.06-1.89 (5 H, m), 1.716 (1 H, m); IR (neat) 2953, 2870, 1744, 1730, 1448, 1435, 1269, 1252, 1130, 1040, 733, 690 cm^{-1}; MS: m/e 288, 286, 254, 256, 207, 175, 147, 119, 105, 91, 77, 65; HRMS: me/ for $C_{12}H_{15}O_3Br$ calcd. 288.01854, measured 288.01790; CMR ($CDCl_3$): 199.575, 170.747, 133.794, 123.598, 75.050, 58.238, 52.194, 43.263, 37.582, 36.892, 21.704, 20.544.

Ethyl 5-bromo-4-methyl-9-oxo-bicyclo[3.3.1]nonane carboxylate **39**

Compound **39** was synthesized using the same procedure and reaction conditions as used in the synthesis of compound **39a.** ^{1}H NMR ($CDCl_3$): 5.751 (1 H, m), 4.244 (2 H, q, J=7.2 hz), 3.355 (1 H, m), 2.617-2.268 (4 H, m), 2.041-1.949 (2 H, m), 1.920 (3 H, s), 1.732-1.659 (1 H, m), 1.303 (3 H, t, J = 7.2 hz); IR (neat) 3030, 2986, 2868, 1740, 1718, 1454, 1265, 1254, 1204, 1042, 1028, 690, 631 cm^{-1}; MS: m/e 302, 300, 258, 256, 221, 201, 175, 149, 119, 105, 91, 77, 65; HRMS: m/e for $C_{13}H_{17}O_3Br$ calcd. 300.03611, measured 300.03591; CMR ($CDCl_3$): 199.554, 170.213, 133.813, 123.675, 75.217, 61.185, 58.078, 43.302, 37.591, 36.906, 21.706, 20.583, 13.743.

Ethyl 4-methyl-5-(1,3-dioxo-3-phenyl)-bicyclo[3.3.0]oct-3-enyl-1 **40**

Compound **40** was prepared using the same procedure and reaction conditions as used in the synthesis of compound **36**. ^{1}H NMR ($CDCl_3$): 15.906

(1 H, s), 7.804 (2 H, d, J=7.5 hz), 7.555 (3 H, m), 6.065 (1 H, s), 5.572 (1 H, s), 3.979 (2 H, m), 3.438 (1 H, m), 2.311 (3 H, m), 1.849 (4 H, m), 1.567 (3 H, s), 1.093 (3 H, t, J=6.9 Hz); MS: m/e 340, 294, 266, 220, 194, 147, 121, 105, 91, 77, 65; HRMS: m/e for $C_{21}H_{24}O_4$ calcd. 340.16746, measured 340.16722; CMR ($CDCl_3$): 200.265, 179.924, 175.972, 139.505, 134.478, 131.892, 128.500, 127.292, 126.719, 94.733, 76.704, 63.080, 60.647, 43.100, 42.662, 30.302, 24.488, 13.699, 13.204.

Methyl 4-Methyl-5-(dimethylphosphonoacetyl)-bicyclo[3.3.0]oct-3-enyl-1-carboxylate **41a**

To a solution of dimethyl methylphosphonate (0.423 g, 3.4 mmol) in 5 mL of THF at -78°C was added n-BuLi (1.36 mL, 3.4 mmol). The solution became a white suspension which was stirred for 15 min. The bromoketone **39a** (0.750 g, 2.62 mmol) in 10 mL of THF was added dropwise. The solution was stirred for 15 min at -78°C and then allowed to slowly warm to 25°C over 1 h. The solution was then cooled to -78°C and quenched with 15 mL of 2N HCl. The aqueous layer was extracted four times with 30 mL ether. The combined extracts were dried and concentrated in vacuo. The residue was purified by chromatography on silica gel using 15:15:1 H:EA:EtOH to afford 0.365 g (49% yield) of ester **41a**. The ester was a colorless oil with R_f =0.24 in 15:15:1 H:EA:EtOH. ^1H NMR ($CDCl_3$): 5.610 (1 H, s), 3.790 (3 H, d, J = 11.4 Hz), 3.767 (3 H, d, J = 11.4 Hz), 3.670 (3 H, s), 3.189 (1 H, m), 3.902 (1 H, m), 2.814 (1 H, m), 2.637 (1 H, m), 2.233 (2 H, m), 1.905-1.458 (7 H, m); IR (neat) 2959, 2872, 1726, 1655, 1439, 1385, 1250, 1032, 804 cm^{-1}; MS: m/e 330, 298, 270, 179, 151, 119, 109, 91, 79, 65; HRMS: m/e for $C_{15}H_{23}O_6P$ calcd. 330.12323, measured 330.12270; CMR

($CDCl_3$): 201.554, 201.471, 176.126, 139.091, 128.021, 79.978, 79.908, 62.477, 52.795, 52.708, 52.447, 52.373, 52.070, 42.900, 42.635, 37.506, 35.646, 30.001, 23.860, 13.036.

4-Methoxy-8-methyltricyclo[3.3.3.0]undec-3-en-2-one **45a**

To a suspension of 10% Pd/C (0.010 g) in 6 mL of MeOH under an atmosphere of hydrogen was added ester **41a** (0.170 g, 0.59 mmol) in 1 mL MeOH. The suspension was stirred at ambient temperature for 72 h. The suspension was then filtered through Celite with MeOH (do not let catalyst become dry!). The methanol solution was concentrated in vacuo. The residue was purified by chromatography on 3:3:1 H:EA:EtOH to afford 0.175 g (100% yield) of **44a**. ^1H NMR ($CDCl_3$): 3.814 (3 H, d, J = 10.8 Hz), 3.776 (3 H, d, J = 11.4 Hz), 3.592 (3 H, s), 3.282 (1 H, dd, J = 16.5, 20.1 Hz), 2.986 (1 H, dd, J = 16.5, 19.8 Hz), 2.682 (1 H, m), 2.310-1.480 (10 H, m), 0.972 (3 H, d, J = 6.9 Hz); IR (neat) 2956, 2878, 1728, 1690, 1455, 1256, 1180, 1135, 1030, 870, 805 cm^{-1}; MS: m/e 332, 301, 277, 245, 217, 151, 121, 109, 93, 79, 55; HRMS: m/e for $C_{15}H_{25}O_6P$ calcd. 332.13888, measured 332.13824; TLC (15:15:a H:EA:EtOH) R_f = 0.24.

Compound **44a** (0.080 g, 0.28 mmol) and potassium t-butoxide (0.078 g, 0.70 mmol) and a crystal of 18-crown-6 were heated at 80°C in 5 mL of toluene for 15 h. The solution was then cooled to 0°C, water was added and the aqueous layer was extracted twice with ether. The combined organic layers were dried and concentrated in vacuo. The residue was purified by chromatography on silica gel using 5:5:1 H:EA:EtOH to afford 0.023 g (30% yield) of compound **45a**. ^1H NMR (neat): 5.150 (1 H, s), 3.812 (3 H, s), 2.1-1.25 (11 H,

m), 1.031 (3 H, d, J = 6.6 Hz); IR (neat) 2957, 2876, 1715, 1603, 1458, 1353, 1228, 1141, 830 cm^{-1}; MS: m/e 206, 178, 165, 152, 137, 124, 105, 91, 77, 65; HRMS: m/e for $C_{13}H_{18}O_2$ calcd. 206.13068, measured 206.13042; TLC (5:1 H:EA) R_f = 0.21.

4-Methoxy-8-methyltricyclo[3.3.3.0]undec-3-en-2-one **45b**

A solution of ester **41a** (0.150 g, 0.45 mmol) and $[Ir(COD)(PCy_3)(pyr)]PF_6$ (0.020 g, 0.025 mmol) in 3 mL of CH_2Cl_2 was charged with an atmosphere of hydrogen. The solution was stirred for 15 h at 25°C. The solvent was removed in vacuo and ether was added. The suspension was passed through a silica gel column with 5:5:1 H:EA:EtOH. The crude product had been quantitatively converted into the bicyclo[3.3.0]octane **44b**. ^1H NMR ($CDCl_3$): 3.802 (3 H, s), 3.765 (3 H, s), 3.620 (3 H, s), 3.081 (1 H, d, J = 21.6 Hz), 3.079 (1 H, d, J = 21.3 Hz), 2.503 (1 H, m), 2.213 (4 H, m), 1.905-1.221 (6 H, m), 0.976 (3 H, d, J = 6.9 Hz); IR (neat) 2957, 2876, 1726, 1699, 1458, 1267, 1032, 872, 800 cm^{-1}; MS: m/e 332, 300, 272, 255, 151, 124, 109, 94, 79, 67, 55; HRMS: m/e for $C_{15}H_{25}O_6P$ calcd. 332.13888, measured 332.13840; TLC (15:15:a H:EA:Ethol) R_f = 0.24.

The crude product **44b** (0.060 g, 0.18 mmol) was dissolved in 5 ml of benzene. To this solution was added 18-crown-6 (5 mg) and KH (18.0 mg, 0.42 mmol). The solution was heated to reflux for 6 h. The solution was cooled, washed with water and concentrated in vacuo. The residue was purified by chromatography on silica gel using 5:1 H:EA to elute the product and 5:5:1 H:EA:EtOH to elute the starting material (0.025 g). Chromatography gave 0.020 g (33% yield) of ketone **45b**. ^1H NMR ($CDCl_3$): 5.041 (1 H, s), 3.815 (3 H, s),

2.2-1.25 (11 H, m), 1.066 (3 H, d, J = 6.6 Hz); IR (neat) 2974, 2865, 1687, 1587, 1355, 1232, 1119, 830, 724 cm^{-1}; MS: m/e 206, 178, 163, 152, 124, 105, 91, 77, 65; HRMS: m/e for $C_{13}H_{18}O_2$ calcd. 206.13068, measured 206.13061; TLC (5:1 H:EA) R_f = 0.21.

4,6-Dimethyltricyclo[3.3.3.0]undec-3-en-2-one **46**

To a solution of enone **45b** (0.005 g, 0.024 mmol) in 1.5 mL THF at 25°C was added MeLi (0.12 mL, 0.15 mmol). The solution was heated to 60°C for 6 h. The solution was cooled to 25°C and 1 mL of 2N HCl was added. The reaction mixture was stirred for 30 min. The aqueous layer was extracted twice with ether. The combined organic layers were dried and concentrated in vacuo. The residue was purified by chromatography on silica gel using 5:1 H:EA to afford 0.003 g (65% yield) of enone **46**. The product was a colorless oil with R_f = 0.38 in 5:1 H:EA. ^1H NMR ($CDCl_3$): 5.666 (1 H, d, J = 0.6 Hz), 2.057 (3 H, d, J = 1.2 hZ), 1.90-1.18 (11 H, m), 1.084 (3 H, d, J = 6.6 Hz); GC-IR 2958, 2878, 1724, 1618, 1459, 1382, 1316, 1268, 1128, 865 cm^{-1}; MS: m/e 190, 175, 162, 148, 133, 120, 105, 91, 77, 65; HRMS: m/e for $C_{13}H_{18}O$ calcd. 190.13577, measured 190.13553.

Ethyl 3-ethyl-5-bromo-9-hydroxy-9-(2-oxo-ethyl)-3-azabicyclo[3.3.1]nonane carboxylate **49**

To a solution of alcohol **48** (1.80 g, 5.01 mmol) in 100 mL of methylene chloride was added 4.0 mL of trifluoroacetic acid. The mixture was stirred at room temperature for 20 min, then cooled to -78°C. Ozone was passed through at -78°C until the reaction was completed (solution became blue). Nitrogen was

passed into the solution to remove excess O_3. Two drops of dimethyl sulfide then were added and the solution was slowly warmed to 0°C. Saturated $NaHCO_3$ (20 mL) was added to the mixture and then aqueous layer extracted with ether. The organic layer was washed with brine, dried and concentrated. The crude product was purified by chromatography on silica gel using 15:1 hexanes:ethyl acetate to provide 750 mg (41.5% yield) of hydroxy aldehyde **49**. HRMS: calcd for $C_{15}H_{24}O_4NBr$ 361.08887, found 361.08836. MS: m/e 363, 361, 318, 316, 282, 238, 208, 192, 164, 136, 58. ^1H NMR: ($CDCl_3$) 1.050 (t, 3 H, J = 7.5 Hz), 1.275 (t, 3 H, J = 6.9 Hz), 2.064 (m, 2 H), 2.375 (m, 4 H), 2.748-3.378 (m, 7 H), 4.145 (q, 2 H, J = 6.9 Hz), 5.016 (s, 1 H), 9.973 (t, 1 H, J = 2.4 Hz). IR: (neat) 3425, 2978, 2935, 1715, 1464, 1367, 1258, 1047, 856, 716 cm^{-1}.

Tricyclic alcohol **50**

A solution of hydroxy aldehyde **49** (180 mg, 0.5 mmol) in 25 mL benzene in a pyrex tube was irradiated using a medium pressure Hg atc lamp for 36 h. The solution then was concentrated in vacua and purified by chromatography on silica gel using 3:1 hexanes:ethyl acetate to afford 50 mg (27.8% yield) of diol **50** and 40 mg of **49**. HRMS: calcd for $C_{15}H_{24}O_4NBr$, calcd. 361.08887, found 361.08877. MS: m/e 363, 361, 348, 346, 282, 264, 236, 220, 208, 107, 77, 58. ^1H NMR: ($CDCl_3$) 1.051 (t, 3 H, J = 6.9 Hz), 1.282 (t, 3 H, J = 7.5 Hz), 1.405 (m, 1 H), 1.499 (s, 1 H), 1.855 (d, 1 H, J = 15.3 Hz), 2.045-2.446 (m, 6 H), 2.640 (s, 1 H), 2.816 (m, 2 H), 2.959 (d, 1 H, J = 10.2 Hz), 3.142 (m, 2 H), 3.972 (d, 1 H, J = 7.2 Hz), 4.187 (q, 2 H, J = 7.2 Hz), 5.212 (s, 1 H); CMR: ($CDCl_3$) 176.547, 80.370, 77.187, 74.439, 72.826, 61.280, 61.145, 54.923, 51, 872, 51.288, 43.906, 38.662, 28.183, 13.950,12.221. IR: (neat) 3456, 2974, 2824, 1703, 1597, 1445,

1256, 1060, 974, 858, 706 cm^{-1}.

Diels-Alder reaction product **51**

To a solution of bromoketone **34** (4.86 g, 15.33 mmol) in 60 mL of ether was added allylmagnesium bromide (18.4 mL, 1.0 M in diethyl ether, 18.4 mmol) at -78°C. The reaction solution was stirred at -78°C for 2 hours and then slowly warmed to 0°C for another 2 hours. The reaction solution was acidified with 2 N HCl, stirred for 0.5 hour and extracted with ether. The aqueous layer was neutralized with saturated $NaHCO_3$ and extracted with ether. The crude product was dried, concentrated in vacuo to provide 5.03 g (91.5% yield) of allyl alcohol **48** as a diastereoisomeric mixture.

The allyl alcohol **48** (1.74 g, 4.85 mmol) and 1,1-dimethoxytetrachlorocyclopentadiene (1.92 g, 7.28 mmol) were heated at 110°C for 14 hours. The crude product was purified by chromatography on silica gel using 10:1 hexanes:ethyl acetate to provide 980 mg (32.4% yield) of **51** and 1.21 g (40.04% yield) of another diastereoisomer **51a.** HRMS: calcd for $C_{23}H_{32}O_5NBrCl_4$ 621.02038, found 621.02180. ^1H NMR: ($CDCl_3$) 0.754 (dd, 1 H, J = 14.7, 11.4 Hz), 1.071 (t, 3 H, J = 6.9 Hz), 1.285 (t, 3 H, J = 7.2 Hz), 1.647 (m, 3 H), 2.142 (dd, 2 H, J = 12.0, 5.7 Hz), 2.354 (m, 5 H), 2.566 (d, 1 H, J = 14.7 Hz), 2.636 (dd, 1 H, J = 11.7, 8.7 Hz), 2.831 (m, 1 H), 2.944 (m, 2 H), 3.068 (d, 1 H, J = 12.3 Hz), 3.164 (d, 1 H, J = 11.7 Hz), 3.535 (s, 3 H), 3.583 (s, 3 H), 4.004 (m, 1 H), 4.223 (m, 1 H), 4.447 (s, 1 H). MS: m/e 623, 621, 574, 572, 492, 490, 456, 252, 238, 210, 182, 136, 108, 71, 58. IR: (neat) 3477, 2972, 2949, 1693, 1605, 1454, 1196, 1119, 911, 773 cm^{-1}. CMR: ($CDCl_3$) 176.851, 129.773, 128.600, 79.322, 74.603, 74.410, 72.946, 64.000, 61.847, 55.227, 54.214,

52.335, 51.460, 51.107, 44.825, 38.985, 36.220, 31.105, 23.147, 14.139, 12.330.

Reduction product **52**

A solution of bromo ester **51** (90 mg, 0.144 mmol), n-Bu_3SnH (49 mg, 0.17 mmol) and AIBN (3.6 mg, 0.022 mmol) in 2 mL of toluene was heated at 130°C for 14 hours. Then the solvent was removed. The crude products were purified by chromatography on silica gel using 10:1 hexanes:ethyl acetate to provide 44 mg (56.1% yield) of reduction product **52**. MS: $CI(NH_3)$ 543. ^{1}HNMR: ($CDCl_3$) 0.756 (dd, 1 H, J = 14.1, 11.1 Hz), 1.054 (t, 3 H, J = 6.9 Hz), 1.258 (t, 3 H, J = 7.2 Hz), 1.415-1.666 (m, 4 H), 1.744 (dd, 1 H, J = 12.0, 3.6 Hz), 1.091 (bs, 1 H), 2.20-2.828 (m, 10 H), 3.065 (d, 1 H, J = 12.0 Hz), 3.533 (s, 3 H), 3.583 (s, 3 H), 3.771 (s 1 H), 4.160 (m, 2 H). CMR: ($CDCl_3$) 177.328, 130.299, 128.089, 111.304, 79.410, 74.670, 72.834, 61.083, 56.076, 54.907, 52.557, 51.943, 51.556, 50.174, 43.804, 42.623, 35.005, 34.217, 32.060, 26.085, 20.136, 14.321, 12.558.

1,2,3,4-Tetrachloro-7,7-dimethoxy-6-(3-bromopropyl)bicyclo[2.2.1]-2-heptene **54**

The 1,1-dimethoxytetrachlorocyclopentadiene (723 mg, 2.73 mmol) and 5-bromopentene (340 mg, 2.28 mmol) were heated at 100°C for 16 h. The crude product was purified by chromatography on silica gel using 15:1 hexanes:ethyl acetate to provide 910 mg (96.8% yield) of **54**. HRMS: calcd for $C_{12}H_{15}O_2Cl_4Br$ 411.89800, found 411.89839. MS: m/e 414, 412, 377, 255, 253, 197, 195, 159, 115, 59. ^{1}H NMR: ($CDCl_3$) 0.852 (m, 1 H), 1.016 (m, 1 H), 1.448 (dd, 1 H, J = 11.1, 3.2 Hz). 1.836 (m, 3 H), 2.514 (m, 3 H), 3.372 (m, 2 H),

3.546 (s, 3 H), 3.592 (s, 3H). CMR: ($CDCl_3$) 129.736, 128.321, 111.530, 78.640, 74.389, 52.467, 51.389, 46.355, 41.479, 32.721, 30.423, 28.466. IR: (neat) 2947, 2845, 1605, 1452, 1196, 910, 777, 621 cm^{-1}.

1,2,3,4-Tetrachloro-7,7-dimethoxy-6-propylbicyclo[2.2.1]-2-heptene **55**

A solution of bromoketal **54** (200 mg, 0.484 mmol), n-Bu_3SnH (155 mg, 0.532 mmol) and AIBN (16 mg, 0.097 mmol) in 24 mL of benzene was stirred at reflux temperature for 16 h after degasing. Then the solvent was removed. The crude product was purified by chromatography on silica gel using 20:1 hexanes:ethyl acetate to provide 137 mg (85.0% yield) of **55**. HRMS: calcd for $C_{12}H_{16}O_2Cl_3{}^{35}Cl^{37}$ 333.98749, found 333.98689. MS: m/e 334, 332, 299, 297, 261, 253, 208, 180, 159, 75, 59. ^1H NMR: ($CDCl_3$) 0.970 (t, 3 H, J = 7.2 Hz), 1.272 (m, 2 H), 1.444 (dd, 1 H, J = 11.1, 3.6 Hz), 1.622 (m, 1 H), 2.486 (m, 3 H), 3.543 (s, 3 H), 3.590 (s, 3 H). CMR: ($CDCl_3$) 129.547, 128.750, 111.709, 79.005, 74.730, 52.580, 51.475, 47.030, 41.639, 31.740, 20.421, 14.078. IR: (neat) 2957, 2874, 1605, 1464, 1379, 1275, 1198, 1136, 999,781 cm^{-1}.

Ethyl 5-allyl-3-ethyl-9-oxo-3-azabicyclo[3.3.1]nonane carboxylate **56**

A solution of bromoketone (18.43 g, 58 mmol), allyl tri-n butyltin (38.40 g, 116.0 mmol), and AIBN (1.9 g, 11.6 mmol) in 60 mL of toluene was stirred at reflux temperature for 16 h. Then the mixture was cooled to 0°C and 100 mL of 1.0 N HCl solution was added. The resulting mixture was stirred for 1 h at room temperature. After the product was extracted with water, the aqueous phase was neutralized with saturated $NaHCO_3$ and extracted with ether. The organic layers were combined, dried, and concentrated. The ketoester **56** (13.58 g, 84.0%

yield) was obtained without additional purification. HRMS: calcd for $C_{16}H_{25}O_3N$ 279.18344, found 279.18348. Ms: m/e 279, 264, 238, 206, 192, 170, 136, 98, 79, 72, 58. ^1H NMR: ($CDCl_3$) 1.090 (t, 3 H, J = 7.2 Hz), 1.288 (t, 3 h, J = 7.2 Hz), 1.504 (m, 1 H), 1.775 (m, 1 H), 2.172 (m, 4 H), 2.386 (q, 2 H, J = 7.2 Hz), 2.528 (m, 1 H), 2.922 (m, 3 H), 3.012 (dd, 1 H, J = 2.1, 10.8 Hz), 3.189 (dd, 1 H, J = 2.1, 11.4 Hz), 4.212 (q, 2 H, J = 7.2 Hz), 5.022 (m, 2 H), 5.770 (m, 1 H). CMR: ($CDCl_3$) 212.479, 171.062, 133.618, 116.793, 64.407, 61.574, 60.873, 58.824, 51.007, 48.719, 39.235, 39.102, 36.721, 20.253, 14.014, 12.545. IR: (neat) 2974, 2929, 2772, 1737, 1716, 1292, 1097, 1007, 915 cm^{-1}.

1-allyl-2-methyl-3-oxobicyclo[3.3.1]nonane **58**

A solution of bromoketone **57** (210 mg, 0.913 mmol), allyl tri-n butyltin (605 mg, 1.83 mmol), and AIBN (30 mg, 0.18 mmol) in 1 mL of benzene was stirred at reflux temperature for 10 h after degasing. The reaction solution was cooled and the solvent was removed. The crude product was purified by chromatography on silica gel using 5:1 hexanes:ethyl acetate to provide 120 mg (68.6% yield) of compound **58**. HRMS: calcd for $C_{13}H_{20}O$ 192.15142, found 192.15141. MS: m/e 192, 151, 109, 86, 67, 55. ^1H NMR: ($CDCl_3$) 1.040 (d, 3 H, J = 6.9 Hz), 1.162 (m, 1 H), 1.410-1.690 (m, 3 H), 1.929 (m, 2 H), 2.120 (m, 3 H), 2.309-2.506 (m, 5 H), 5.089 (m, 2 H), 5.820 (m, 1 H). IR: (neat) 3069, 2978, 2921, 2878, 1700, 1635, 1445, 1375, 1190, 995, 905 cm^{-1}.

Ethyl 3-ethyl-5-(2-oxoethyl)-9-oxo-3-azabicyclo[3.3.1]nonane carboxylate **66**

Trifluoroacetic acid (98 mg, 0.86 mmol) was added to asolution of ketoester **56** (200 mg, 0.72 mmol) in 20 mL of methylene chloride. The mixture was stirred

for 10 min at room temperature, then cooled to -78°C. Ozone was passed through at -78°C until the reaction was completed (solution became blue); then nitrogen was passed into the solution to remove excess O_3. Then two drops of dimethyl sulfide was added. The solution was slowly warmed to 0°C and 5.0 mL of saturated $NaHCO_3$ was added. The product was extracted with ether, washed with brine, dried and concentrated. The crude product was purified by chromatography on silica gel using 4:1 hexanes:ethyl acetate. Pure ketoaldehyde **66** (190 mg) was obtained in 94% yield. HRMS: calcd for $C_{15}H_{23}O_4N$ 281.16271, found 281.16325. MS: m/e 281, 252, 238, 195, 167, 136, 93, 71, 58. ^1H NMR: ($CDCl_3$) 1.103 (t, 3 H, J = 7.2 Hz), 1.291 (t, 3 H, J = 7.2 Hz), 1.951 (m, 1 H), 2.422 (m, 9 H), 2.935 (m, 2 H), 3.173 (m, 2 H), 4.221 (q, 2 H, J = 7.2 Hz), 9.810 (s, 1 H). CMR: (CDCl3) 211.357, 200.441, 170.487, 64.448, 61.321, 60.953, 58.424, 50.672, 49.201, 47.712, 39.670, 36.417, 20.186, 13.906, 12.359. IR: (neat) 2973, 2930, 2813, 1733, 1716, 1455, 1366, 1258 cm^{-1}. TLC: (4:1 H:EA) Rf = 0.31.

Tricyclic hemiketal **67**

To a solution of ketoaldehyde **66** (1.85 g, 6.58 mmol) in 150 mL of benzene was added 1-triphenylphosphoranylidene-2-propanone (2.51 g, 7.90 mmol). The reaction mixture was heated at reflux in benzene for 36 h. After removing the benzene, 150 mL of ether was added. The suspension was filtered, and the ether solution was acidified with 2 N HCl, and extracted with ether. The aqueous layer was neutralized with saturated $NaHCO_3$ and extracted with ether. The crude product was dried, concentrated, and purified by chromatography on silica gel using 5:1 hexanes:ethyl acetate to provide 1.83 g (82.0% yield) of hemiketal

67. HRMS: calcd for $C_{18}H_{29}O_5N$ 339.20457, found 339.20406. MS: m/e 339, 321, 296, 278,264, 252, 238, 220, 116, 136, 71, 58. ^1H NMR: ($CDCl_3$) 1.036 (t, 3 H, J = 7.2 Hz), 1.266 (t, 3 H, J = 7.2 Hz), 1.870-1.483 (m, 7 H), 1.983 (dd, 1 H, J = 11.4, 2.1 Hz), 2.164 (s, 3 H), 2.264 (m, 2 H), 2.455 (dd, 1 H, J = 11.1, 2.1 Hz), 2.680 (m, 3 H), 3.056 (m, 2 H), 4.170 (m, 2 H), 4.531 (m, 1 H), 5.123 (s, 1 H). CMR: ($CDCl_3$) 207.766 (s), 175.976 (s), 103.623 (s), 73.843 (d), 60.975 (t), 60.546 (t), 55.834 (t), 52.138 (t),51.551 (t), 49.173 (s), 45. 502 (s), 40.078 (t), 34.100 (t), 32.007 (t), 30.958 (q), 21.237 (t),13.912 (q), 12.481 (q). IR: (neat) 3441, 2970, 2933, 1732, 1711, 1700, 1557, 1455, 1263, 1079, 1038, 955, 871 cm^{-1}.

Ethyl 3-ethyl-5-(4-oxo-2-pentenyl)-3-azabicyclo[3.3.1]nonane carboxylate **68**

To a solution of hemiketal **67** (200 mg, 0.59 mmol) in 25 mL of THF at 25°C was added 10 drop of concentrated sulfuric acid with stirring. The solution was stirred overnight at room temperature and then added to 10 mL of 2 N NaOH solution. The resulting mixture was stirred for 5 min extracted with ether and washed with water. Organic layer was dried, filtered and concentrated in vacuo to provide 189 mg (100% yield) of pure diketone **68**. HRMS: calcd for $C_{18}H_{27}O_4N$ 321.19401, found 321.19374. MS: m/e 321, 278, 252, 220, 192, 147, 136, 71, 58. ^1H NMR ($CDCl_3$) 1.092 (t,3 H, J = 7.2 Hz), 1.299 (t, 3 H, J = 7.2 Hz), 1.800 (m, 1 H), 2.247 (s, 3 H), 2.290 (m, 7 H), 2.969 (m, 2 H), 3.210 (m, 1 H), 4.236 (q, 2 H, J = 7.2 Hz), 6.047 (d, 1 H, J = 15.9 Hz), 6.806 (dt, 1 H, J = 15.8, 7.8 Hz). IR (neat) 2973, 2931, 2811, 1732, 1713, 1674, 1454, 1362, 1257, 1176, 986, 877 cm-1. CMR ($CDCl_3$) 211.975, 198.140, 170.867, 143.495, 134.043, 64.710, 61.514, 61.132, 58.873, 51.000, 49.427, 39.625, 38.161, 26.743, 26.954,

20.314, 14.101, 12.585.

Tetracyclic ketone **71**

To a solution of diketone **68** (1.10 g, 3.43 mmol) in 2 mL of toluene was added 1-(trimethylsilyloxy)-1,3-butadiene (1.22 g, 8.55 mmol). The solution was heated at 260°C for 10 hours. Then the solvent was removed. The crude product was purified by chromatography on silica gel using 10:1 hexanes:ethyl acetate to provided 1.12 g (70.57% yield) of a diastereoisomeric mixture of **69** and **70**. HRMS: calcd for $C_{25}H_{41}NO_5Si$ 463.27540, found 463.27562.

To a solution **69** and **70** (70 mg, 0.15 mmol) in 3 mL of benzene at 0°C was added dropwise a solution of potassium hexamethyldisiliazide in toluene (504 mg, 15% in toluene, 0.38 mmol). After stirring for 10 min in a cool water bath and then slowly warming to room temperature for another 10 min, 1 mL of 2 N HCl was added to the reaction mixture at 0°C. Stirring was continued for 5 minutes. The resulting solution was extracted with water. The aqueous layer was neutralized with saturated $NaHCO_3$ and extracted with ether. The crude product was dried, filtered, concentrated and purified by chromatography on silica gel using 3:1 hexanes : ethyl acetate to provide 38 mg (67.8 % yield) of **71.** HRMS calcd for $C_{22}H_{31}NO_4$ 373.22444, found 373.22531. ^1H NMR ($CDCl_3$) 1.042 (m, 4 H), 1.296 (t, 3 H, J = 6.3 Hz), 1.527 (m. 2 H), 1.791 (m, 2 H), 2.120 (m, 1 H), 2.305 (m, 5 H), 2.540 (m, 1 H), 2.771 (m, 4 H), 2.940 (m, 1 H), 3.280 (m, 1 H), 3.416 (d, 1 H, J = 13.2 Hz), 4.210 (q, 2 H, J = 6.9 Hz), 4.535 (s, 1 H), 5.595 (m, 2 H), 6.973 (s, 1 H). MS: m/e 373, 354, 326, 298, 280, 252, 220, 195, 165, 105, 91, 72, 58. IR: (neat) 3466, 2978, 2934, 1732, 1697, 1666, 1458, 1393, 1261, 1022,

1022, 911, 700 cm^{-1}. CMR ($CDCl_3$) 198.343, 176.343, 137.375, 133.585, 130.572, 122.346, 73.793, 61.578, 61.070, 56.904, 52.714, 51.845, 48.079, 44.719, 40.576, 33.042, 30.967, 30.121, 27.061, 19.897, 14.201, 12.563.

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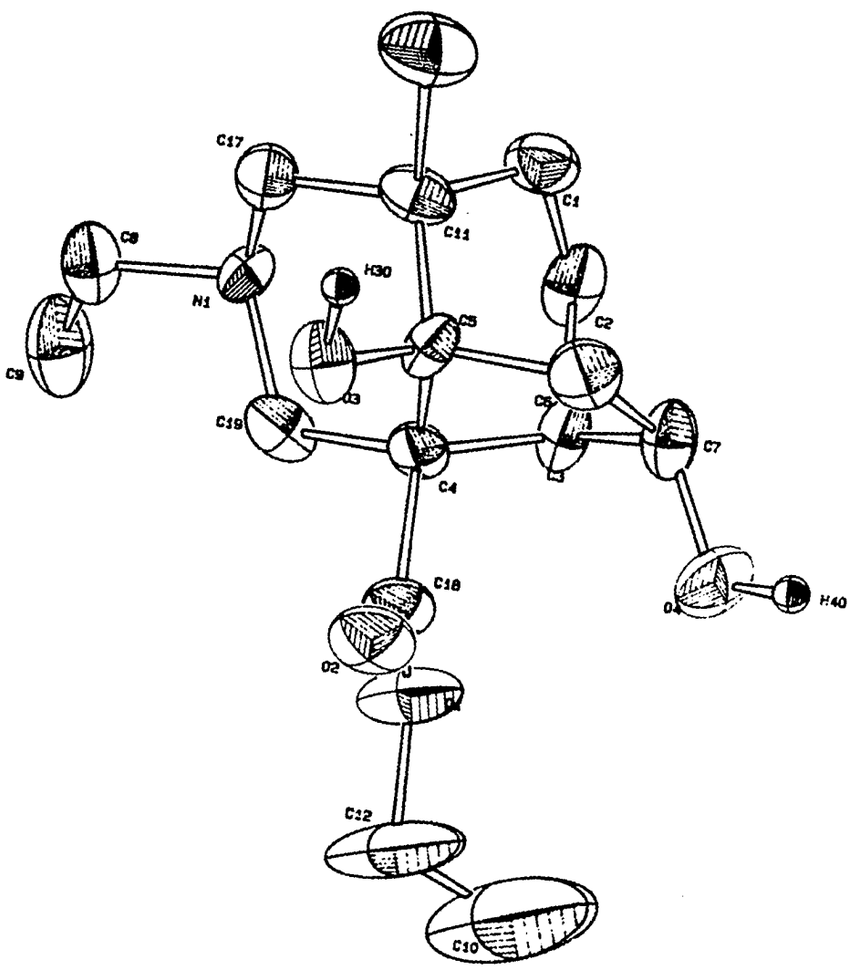
APPENDIX

X-ray Crystal Structure of 50 (Hydrochloride Salt)

Crystal Data

Empirical Formula	$[BrC_{15}N_1O_4H_{24}]Cl \cdot CCl_2H_2$
Formula Weight	481.64
Crystal Color, Habit	transparent, cube
Crystal Dimensions (mm)	0.500 x 0.500 x 0.500
Crystal System	orthorhombic
No. Reflections Used for Unit Cell Determination (2θ range)	25 (14.0 - 35.0°)
Omega Scan Peak Width at Half-height	0.43
Lattice Parameters:	
a	13.250(4)Å
b	16.144(6)Å
c	9.570(4)Å
V	2047(1)Å^3
Space Group	$P2_12_12_1$ (#19)
Z value	4
D_{calc}	1.563 g/cm^3
F_{000}	984
$\mu_{(MoK\alpha)}$	24.01 cm^{-1}


C17
C1
C11
C8
H30
N1
C2
C5
C9
O3
C19
C6
C7
C4
C3
C18
O4
H40
O2
C12
C10

ACKNOWLEDGEMENTS

I would like to express my gratitude to my major professor Dr. George A. Kraus for his steadfast guidance of the research and assistance in preparation of this manuscript.

I am grateful to the American Cyanamid Company and the National Institutes of Health for financial support of this work.

I would like to express my gratitude to professor Yaowu Ji for his advice and encouragement during my study in Zhengzhou University.

I also wish to express my gratitude to my parents, my brothers and sisters. It is impossible for me to pursue a Ph.D. degree without their love, and support.

A very special thanks goes to the most important people of my life — my wife, Xianping, my son, Yan, and my daughter, Eileen. They give me the warmest love, endless happiness, and hope.