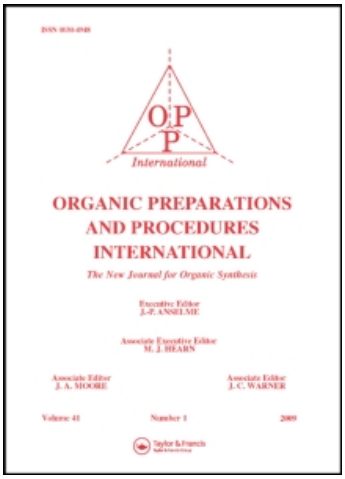

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FURANOSESQUITERPENE SYNTHESIS. AN UPDATED REVIEW

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INTRODUCTION

Furanosesquiterpenes are a major subcategory of terpenoid natural products, being found in both the terrestrial and marine environments. As a class, the presence of the furan ring does not confer any general form of biological activity to the metabolites. Instead, the metabolites show the usual varieties of activities not linked to any particular structural features. Syntheses of metabolites in this category tend to be isolated works, with little general methodology concerning the construction of sesquiterpenic furans having arisen. Frequently, however, the synthesis of a compound in this class has served to showcase methodology developed for the synthesis of substituted furans.

This review will cover the years between 1980 and 1991 inclusive, picking up where the review by Heathcock[1] left off. A more recent review of polycyclic sesquiterpene synthesis[2] only minimally overlaps with this effort. There is also some overlap with our recent near-comprehensive review of marine natural products synthesis.[3]

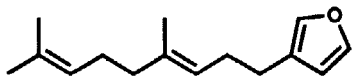
Reviews of this nature tend to be compilations that degenerate into "...compound **X** was converted to compound **Y** with reagent **Z** and then converted to...." and so on. However, a certain amount of description of scheme content must be tolerated. We expect the text to be read by those whose primary field of interest is not synthesis and who, perhaps, need a guide through the morass of synthesis detail. We fully expect those who are organic synthesis aficionados to skip over the text and concentrate on the schemes. We have placed as much information over the arrows as we think important for "skimmers" of this type. Finally, we have organized the syntheses according to number of rings (including the furan) and then according to increasing ring size, attempting to keep structurally similar compounds together for easier comparison of strategies and pathways.

I. COMPOUNDS WITH ONLY A FURAN RING

DENDROLASIN

Dendrolasin (**1**) was originally isolated from the ant *Lasius (Dendrolasius) fuliginosus* in 1956.[4] The structure was assigned using the classical methodology of the time including IR and UV

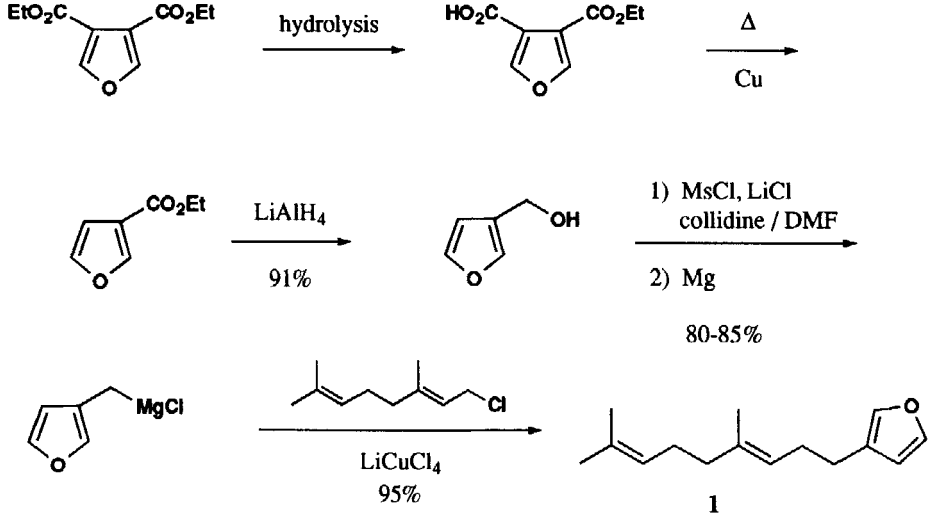
spectroscopy in conjunction with chemical degradation techniques. A subsequent report showed dendrolasin to be the first furan derivative ever isolated from an animal.[5] The structure was shown to



1

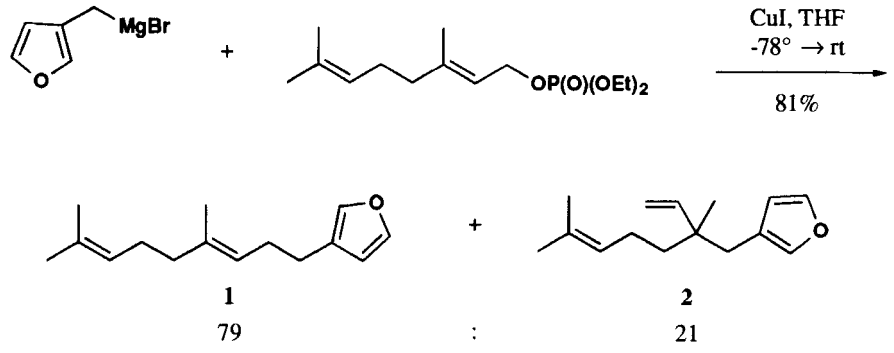
be 1, the simplicity of which has resulted in many syntheses of this molecule. Many of these works were designed to highlight new methods of preparation of substituted furans.

A major approach to the preparation of dendrolasin has involved metal-mediated coupling of 3-furyl organometallics with geranyl halides and related substances. Many of the approaches suffer from lack of regiospecificity in the coupling, however. The major carbon-carbon bond formation in a synthesis reported by Tanis was achieved by a copper-catalyzed Grignard coupling of geranyl chloride and 3-furylmagnesium chloride (Scheme 1).[6] Butsugan reported a similar coupling approach to

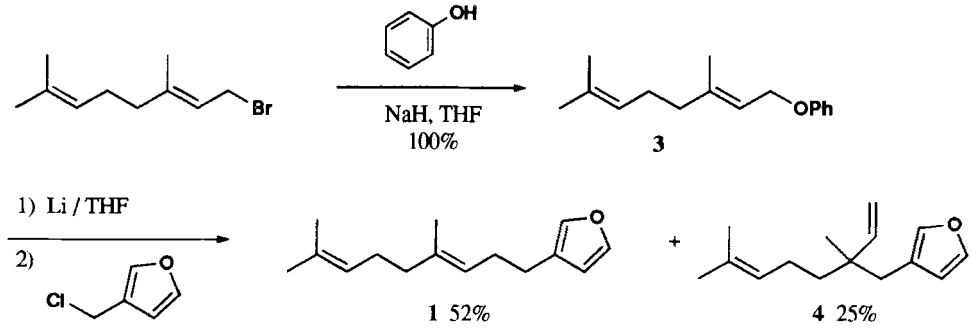


Scheme 1. *Tanis Dendrolasin Synthesis*

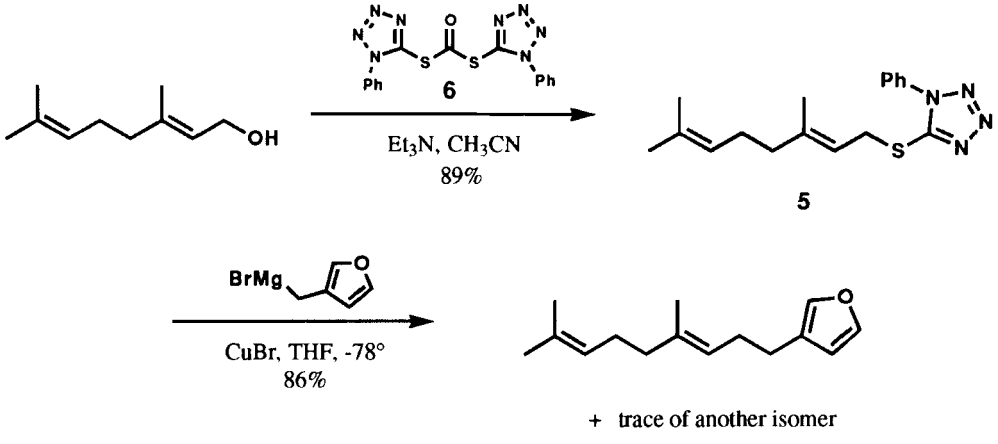
dendrolasin in 1982 (Scheme 2).[7] This approach involved the copper-catalyzed coupling of 3-furylmagnesium bromide and geranyl phosphate. Unlike the coupling by Tanis, this reaction was not regiospecific and resulted in a mixture of 1 and 2. Another coupling approach was reported by Lanzetta (Scheme 3) which involved reaction between geranyllithium and 3-furyl chloride.[8] Geranyllithium was prepared by reductive cleavage of the corresponding allyl phenyl ether 3. As in the coupling reported by Butsugan, there was no observed scrambling of trisubstituted olefin geometry, however regioisomer 4 was obtained in addition to dendrolasin. Ogura demonstrated the utility of an allylic sulfide in a coupling reaction (Scheme 4).[9] The allylic sulfide 5 was conveniently



Scheme 2. *Butsugan Dendrolasin Synthesis*



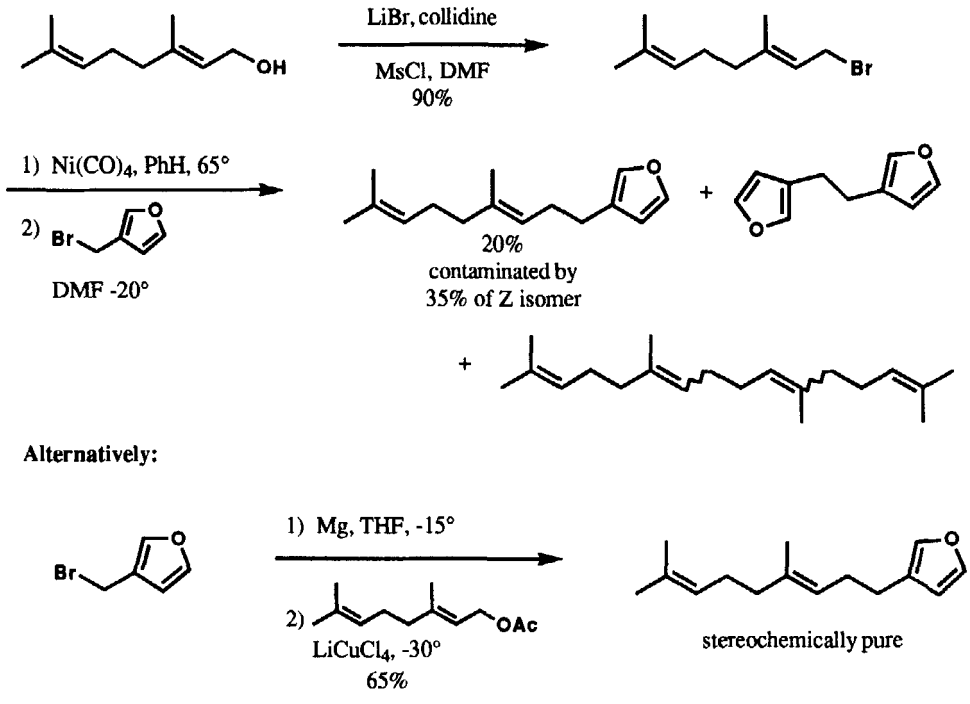
Scheme 3. *Lanzetta Dendrolasin Synthesis*



Scheme 4. *Ogura Dendrolasin Synthesis*

prepared from the reaction of geranyl alcohol and the dithiocarbonate **6**. This intermediate smoothly underwent a copper-catalyzed coupling with 3-furylmagnesium bromide to give dendrolasin and only a trace of another isomer. In what can only be described as an uncontrolled coupling, Rossi reported a

synthesis of **1** *via* the $Ni(CO)_4$ promoted allylic bromide coupling process shown in Scheme 5.[10] The same report described the copper-catalyzed coupling of 3-furylmagnesium bromide and geranyl

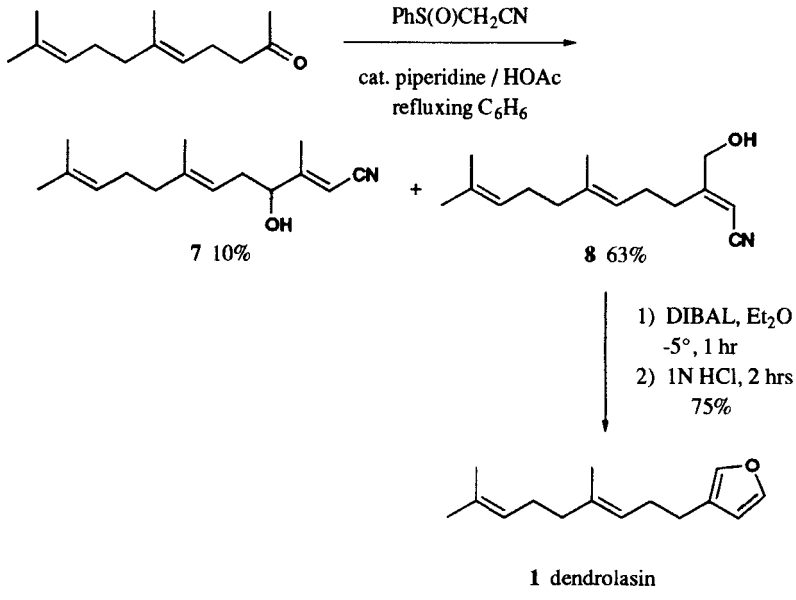


Scheme 5. *Rossi Dendrolasin Syntheses*

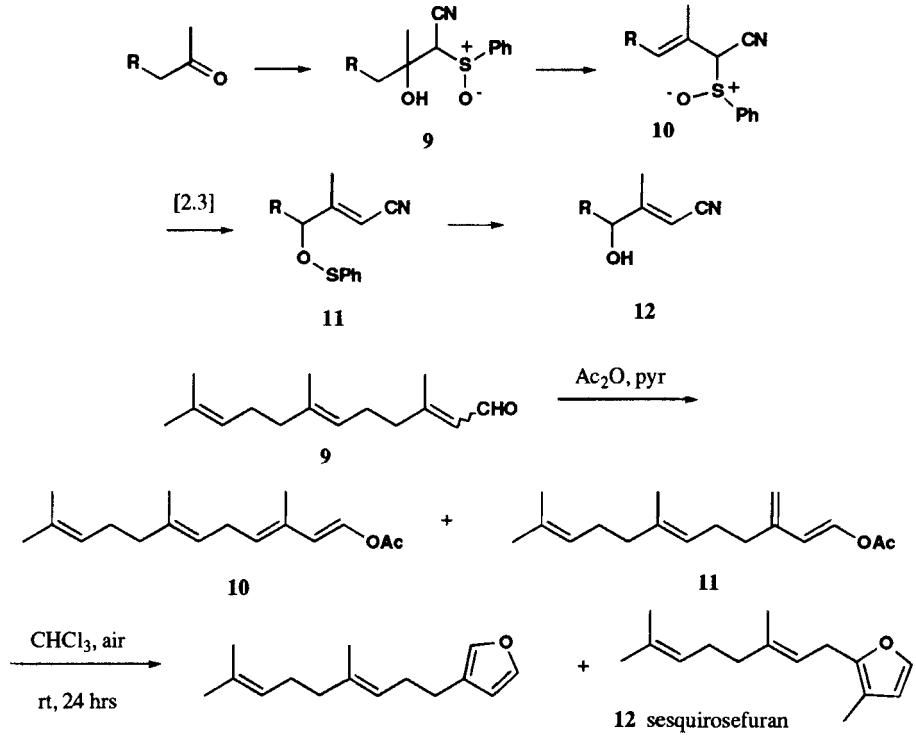
acetate. This was a much more selective reaction, producing a 65% yield of dendrolasin that was reported to be regio- and stereochemically pure.

A variety of approaches have used the construction of a 3-substituted furan as the focal point. In 1981, Nokami presented a synthesis of dendrolasin that displayed such a method.[11] In this synthesis (Scheme 6) the cyanoalcohols **7** and **8** were prepared from the condensation of phenylsulfinylacetonitrile and geranylacetone in 10% and 63% yields respectively. The process probably involves an intermediate allylic sulfoxide **10** which undergoes [2.3] sigmatropic rearrangement to **11** followed by S-O cleavage to give the γ-hydroxy-α,β-unsaturated nitrile (**12**). Isomer **8** could then be easily converted to dendrolasin by a DIBAL reduction and acidic hydrolysis.

In 1982, Tada approached the synthesis of dendrolasin from a biomimetic standpoint (Scheme 7).[12] In this synthesis, farnesal (**9**) was acylated to form the mixture of enol acetates **10** and **11**. These were then allowed to air oxidize which produced a 4% yield of a mixture of dendrolasin and sesquirosefuran **12**. It was found from the separated enol acetates that only the enol acetate **10** underwent cyclization to furan-containing products.



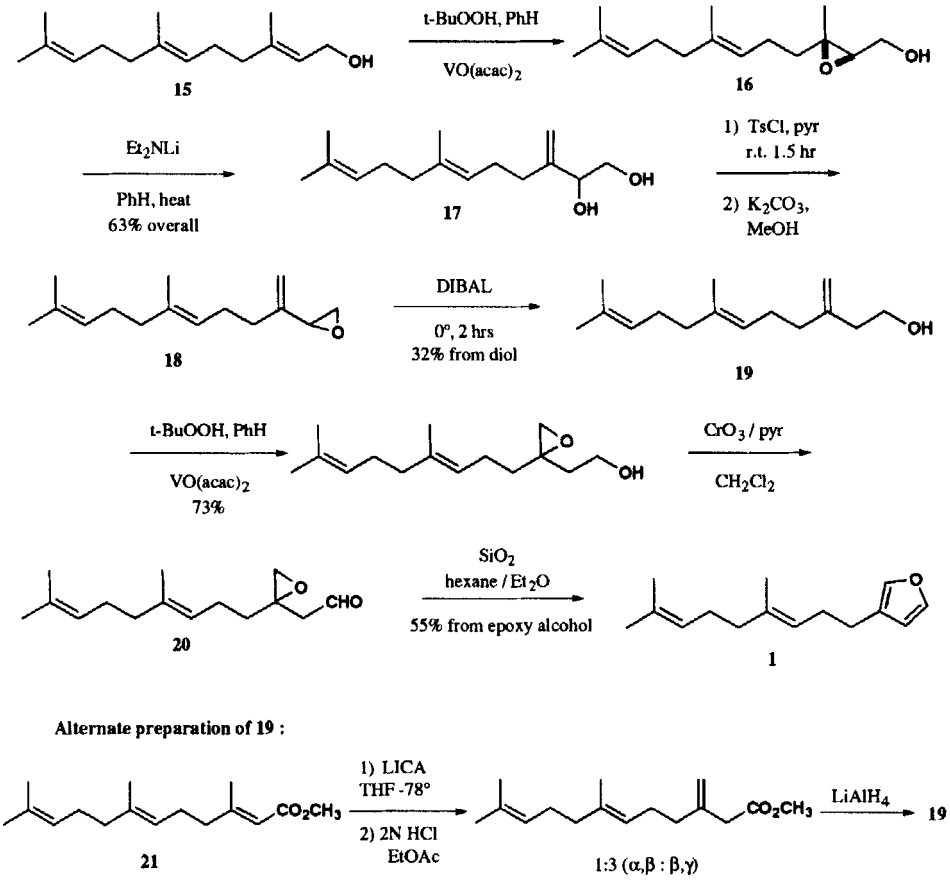
Scheme 6. *Nokami Dendrolasin Synthesis*



4% yield as a 1:5 inseparable mixture

Scheme 7. *Tada Dendrolasin Synthesis*

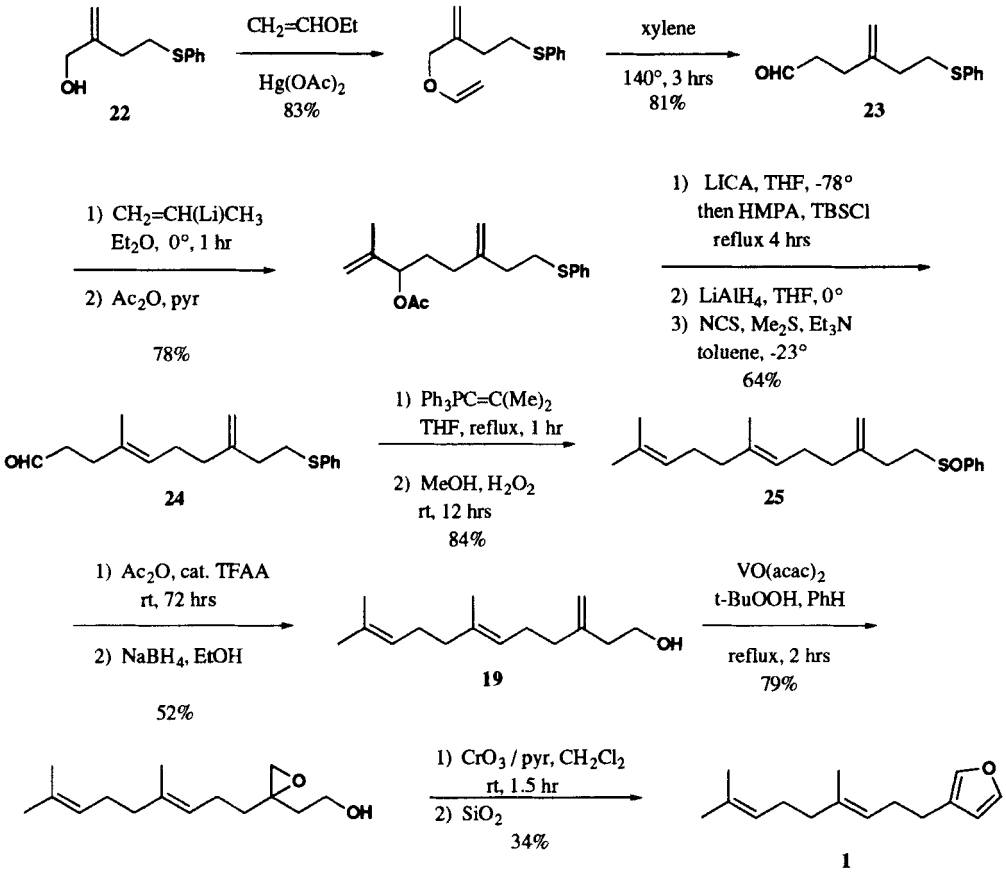
Also in 1982, Lee reported a multistep approach to dendrolasin in which the two key transformations were well-precedented selective epoxidations (Scheme 8).[13] The triene **15** was selectively



Scheme 8. *Lee Dendrolasin Synthesis*

epoxidized to give **16** which was converted to the diol **17** by treatment with lithium diethylamide. Tosylation of the primary alcohol and displacement afforded the epoxide **18**. A subsequent hydride reduction of the epoxide provided **19**, presumably the product of a Lewis acid promoted opening, albeit in low yield. Epoxidation of the homoallylic alcohol and oxidation gave the epoxyaldehyde **20** which was cyclized to the furan under the customary acidic conditions to complete the synthesis of **1**. An alternate preparation of intermediate **19** was described in a more recent work which shortens the route and increases the overall yield somewhat.[14] This was accomplished by deprotonation of the α,β unsaturated ester **21** with lithium isopropylcyclohexylamide followed by a kinetic quench.

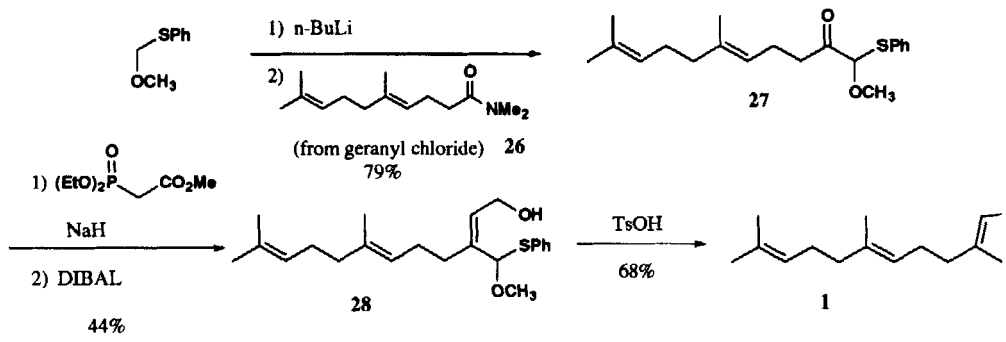
Otera has reported two syntheses of dendrolasin. One was a multistep approach[15] that was identical to the Lee route, utilizing the homoallylic alcohol **19** (Scheme 9). This substance was prepared essentially from scratch with good stereoselectivity through a series of sigmatropic



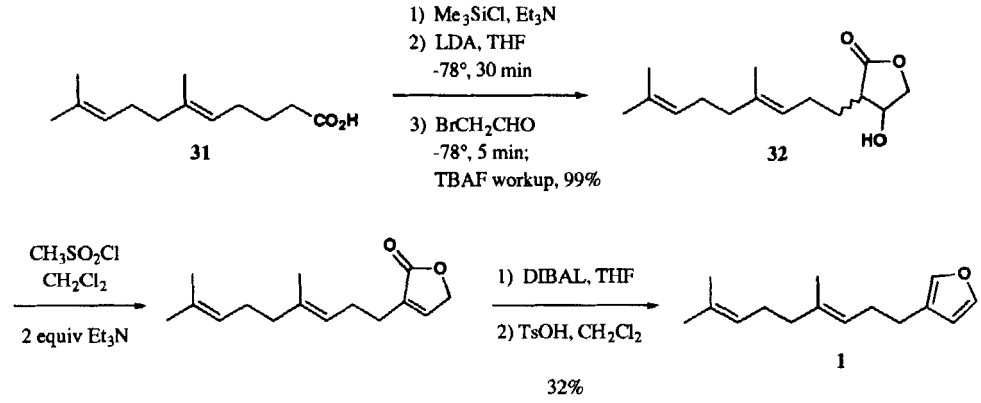
Scheme 9. *Otera Dendrolasin Synthesis*

rearrangements. The allylic alcohol **22** was Claisen rearranged to the aldehyde **23**. Reaction with isopropenyllithium and acetylation was followed by an Ireland-Claisen rearrangement to form the γ,δ-unsaturated acid which was esterified, reduced and oxidized to the aldehyde **24**. The terminal unit was introduced *via* a Wittig reaction. Oxidation of the thioether gave sulfoxide **25** which was followed by Pummerer rearrangement giving the alcohol **19**. From here the pathway intersects that of Lee. The second synthesis reported by Otera was accomplished in fewer steps and a higher overall yield (Scheme 10).[16] The anion of methoxy(phenylthio)methane was treated with the amide **26** (obtained from geranyl chloride) to produce the ketoacetal **27**. Wadsworth-Emmons reaction and reduction gave the alcohol **28** which was cyclized to dendrolasin.

Kraus reported a synthesis of dendrolasin in 1983 based on methodology developed for the synthesis of β-hydroxybutyrolactones (Scheme 11).[17] The lactone **32** was prepared as a 1:1 diastereomeric mixture from the known acid **31** by the reaction of the enolate of the TMS ester with bromoacetaldehyde and subsequent alkylative cyclization. The lactone **32** was then converted to the furan by a standard sequence resulting in an overall 32% yield of dendrolasin.

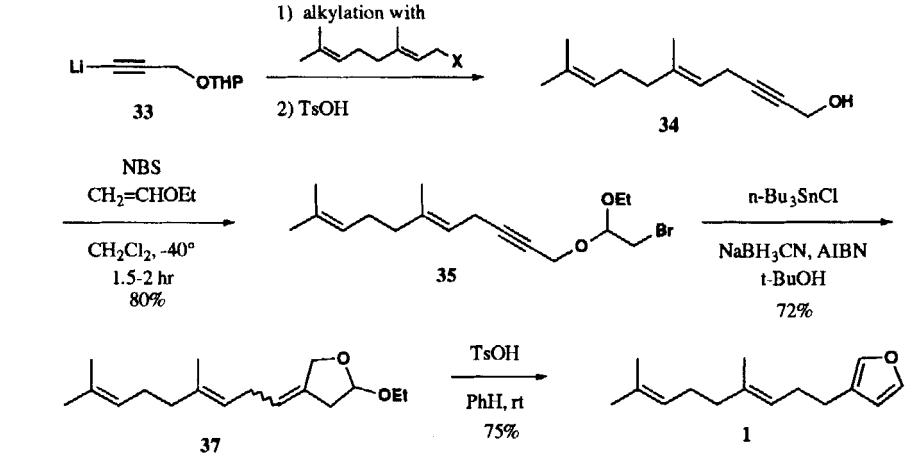


Scheme 10. *Otera Dendrolasin Synthesis*



Scheme 11. *Kraus Dendrolasin Synthesis*

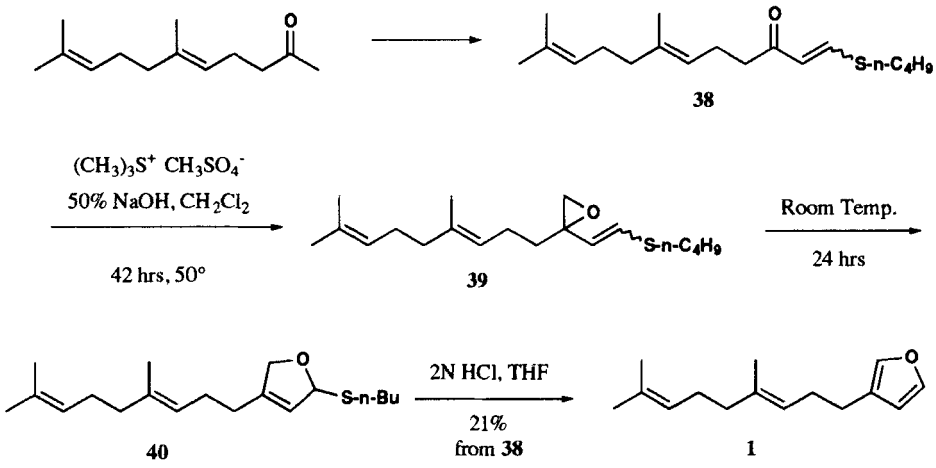
Srikrishna reported a synthesis of **1** which revolved around the construction of the furan ring (Scheme 12).[18] The substrate **35** was prepared by alkylation of a geranyl halide with the known



Scheme 12. *Srikrishna Dendrolasin Synthesis*

lithioalkyne **33**. Reaction of the propargylic alcohol **34** with ethyl vinyl ether in the presence of NBS afforded the bromoacetal **35** which underwent radical cyclization upon treatment with Bu_3SnH precursors to form the lactol **37**. Treatment with TsOH then gave **1**.

The synthesis by Schore (Scheme 13) demonstrated an improvement in a substituted furan

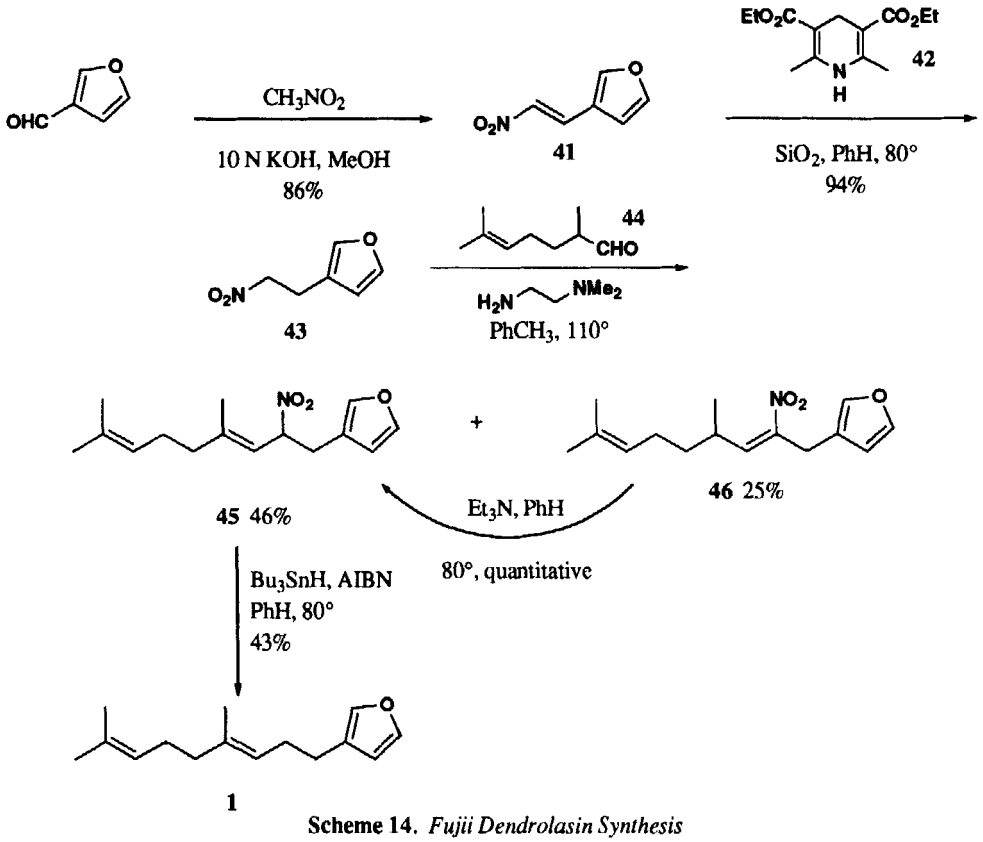


Scheme 13. *Schore Synthesis of Dendrolasin*

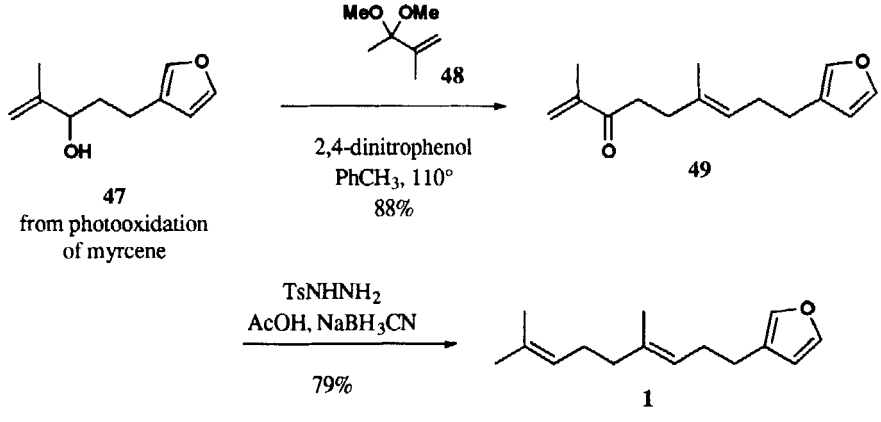
synthesis[19] originally developed by Spencer.[20] Treatment of the α-thiomethylene ketone **38** with trimethylsulfonium methylide under phase-transfer conditions gave the epoxide **39**. When allowed to stand at room temperature, such compounds rearrange to the dihydrofuran (**40**). Subsequent treatment with acid produces the furan, in this case resulting in a 21% yield of dendrolasin from **38**.

Two approaches other than the Otera synthesis (Scheme 9) have dealt with the synthesis of the side chain. Fujii demonstrated the C=C reduction of nitro olefins using the Hantzsch Ester and applied the reaction to a synthesis of **1** (Scheme 14).[21] The nitro olefin **41** was formed by Henry reaction of nitromethane and 3-furaldehyde. Reduction with Hantzsch ester **42** in the presence of silica gel gave the nitroalkane **43** in 94% yield. A second Henry reaction with aldehyde **44** resulted in a mixture of olefin isomers **45** and **46**. However, **46** could be converted to the desired isomer quantitatively by treatment with Et_3N. Removal of the nitro group was accomplished utilizing Bu_3SnH in moderate yield to provide dendrolasin in an overall 25% yield. The most recent synthesis of dendrolasin, reported by Baeckstrom in 1991, demonstrates the use of a Claisen rearrangement (Scheme 15).[22] The allylic alcohol **47** available by oxidation of myrcene[23] was heated with acetal **48** in the presence of a weak acid to induce [3.3] sigmatropic rearrangement to the enone **49**. This was deoxygenated in a one-pot procedure to yield dendrolasin in 70% overall yield from **47**.

Perhaps the most straightforward solutions to this problem involve simple alkylation processes utilizing readily available geranyl electrophiles. Masaki synthesized dendrolasin using such an approach (Scheme 16).[24] Geranyl bromide was treated with the anion of 3-furyl-p-tolylsulfone (**52**) to produce the alkylation product **53**. Dissolving metal reduction removed the sulfone and afforded **1** in

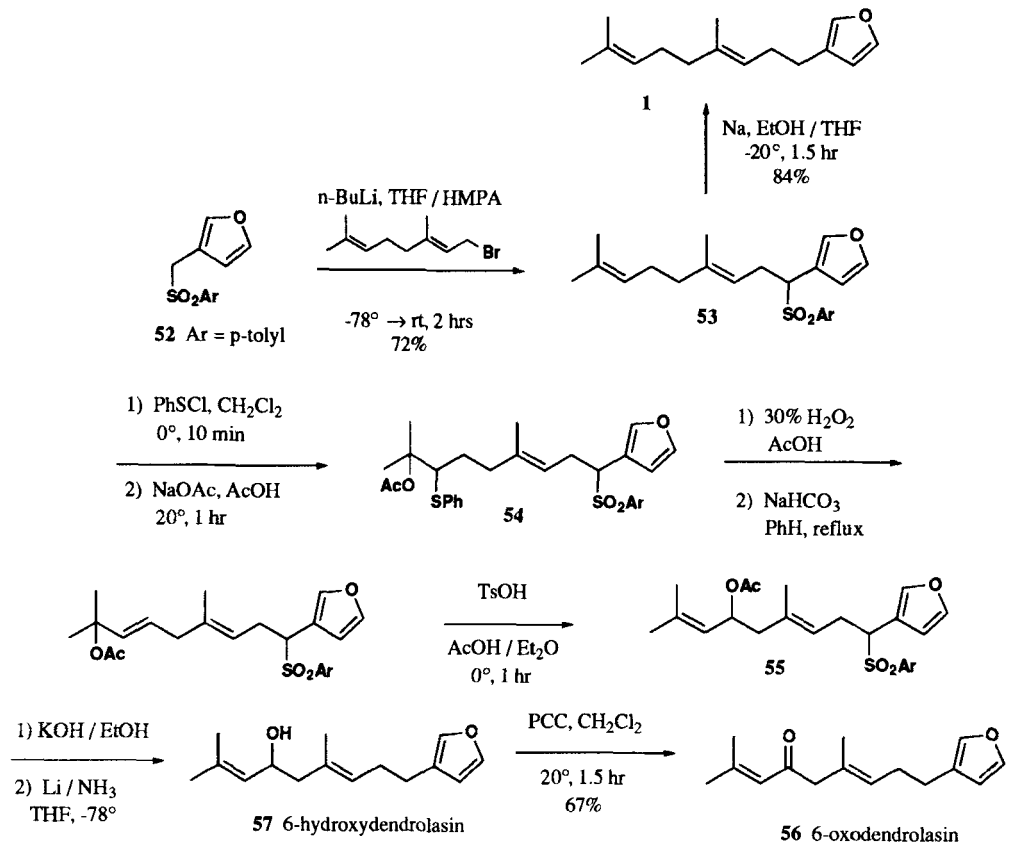


Scheme 14. *Fujii Dendrolasin Synthesis*



Scheme 15. *Bäckstrom Dendrolasin Synthesis*

60% overall yield. In addition to dendrolasin, two naturally occurring oxidized dendrolasin derivatives were also prepared. 6-Oxo- and 6-hydroxydendrolasin (**56** and **57**)[25] were produced by oxidation of the sulfone intermediate **53**. Reaction of the terminal olefin with PhSeCl followed by solvolysis of the

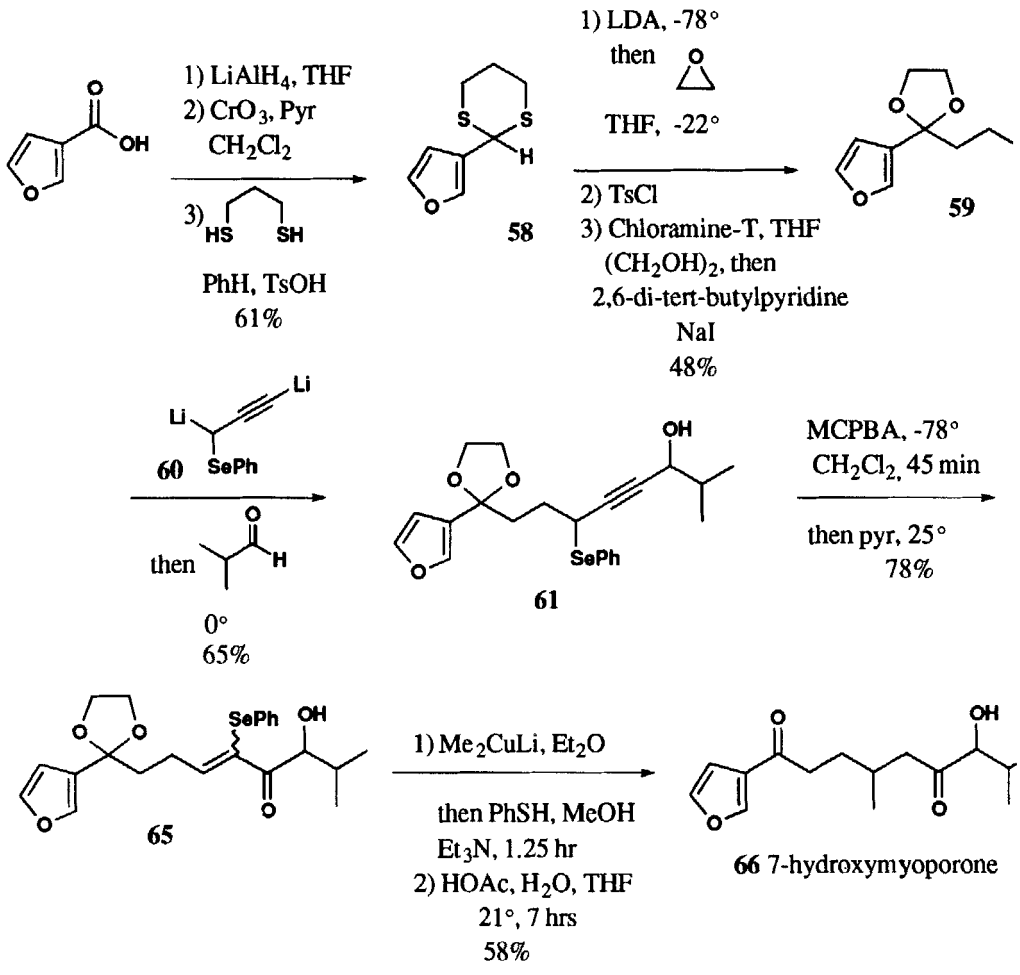


Scheme 16. *Masaki Dendrolasin Synthesis*

chloride resulted in the acetate **54**. Elimination of the phenylselenide was achieved by oxidation and treatment with base. The resulting allylic acetate underwent rearrangement to the internal acetate **55** upon treatment with TsOH. Acetate hydrolysis and reductive desulfurization afforded 6-hydroxydendrolasin (**57**). Oxidation with PCC resulted in a 67% yield of 6-oxodendrolasin **56**.

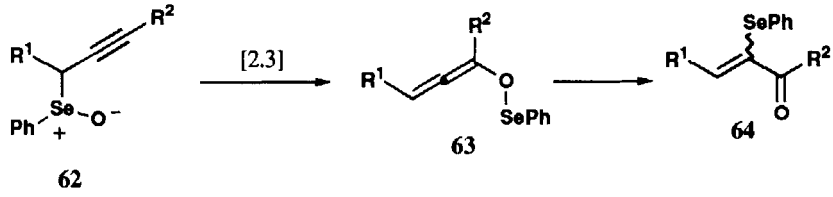
7-HYDROXYMYOPORONE

Reich has synthesized racemic 7-hydroxymyoporone[26] (**66**) and 7-*epi*-hydroxymyoporone using selenium-based methodology developed in the early 1980's. The metabolite is produced by sweet potatoes in response to invasion by fungi. The relative stereochemistry of the natural product is not known with certainty and the synthesis did nothing to rectify this situation. Nevertheless the synthesis showcases an interesting rearrangement-isomerization of propargylic selenoxides (Scheme 17).[27] 3-Furoic acid was converted to the dithiane **58** which was deprotonated with LDA and alkylated with ethylene oxide. The intermediate alcohol was tosylated, the dithiane was exchanged for dioxolane and converted to the iodide **59**. Displacement of the iodide with the propargylic selenium reagent **60** and quenching with isobutyraldehyde produced intermediate **61** in an efficient one flask operation. Oxidation to the selenoxide (**62**, below) with MCPBA was followed by in situ



Scheme 17. *Reich 7-Hydroxymyoporone Synthesis*

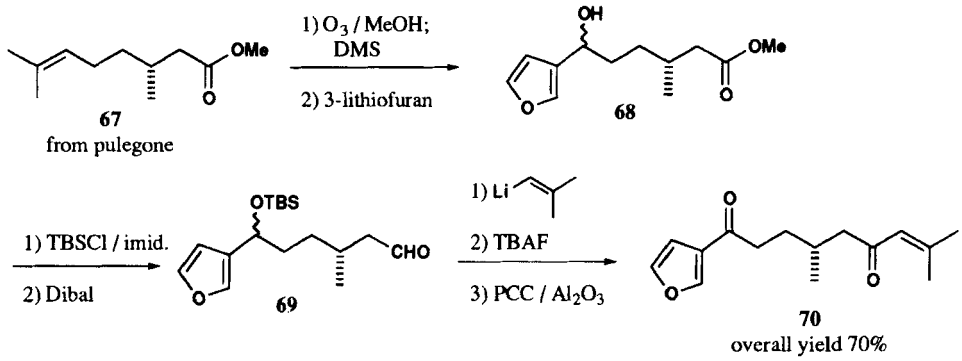
[2.3]-sigmatropic rearrangement presumably to an allenyl selenate (**63**) which was not detected, but isomerized to an E/Z mixture of the α-phenylselenenylketone (**65** in Scheme 17). Lithium



dimethylcuprate addition and deselenation was followed by final deketalization to give a 70:30 mixture of diastereomers. The minor isomer was found to be spectroscopically identical to natural 7-hydroxymyoporone.

MONOCYCLIC EUMORPHA METABOLITE 70

As part of the structure elucidation of metabolites from the South African composite *Eumorpha prostata*, Bohlmann elected to synthesize several furanosesquiterpenes.[28,29] The most abundant metabolite is the monocyclic compound **70** which was produced in optically active form to confirm the absolute configuration at the secondary methyl-bearing stereogenic center (Scheme 18).



Scheme 18. *Bohlmann Synthesis of Eumorpha Metabolite 70*

Related bicyclic *Eumorpha* metabolites are discussed in the next section. R-(+)-Pulegone was converted to the ester **67** according to literature precedent. Ozonolysis and reaction with 3-lithiofuran produced the alcohol mixture **68**. The alcohol was blocked and the ester converted to aldehyde **69**. Reaction with isobutenyllithium put in the final C-C bond and the metabolite **70** was obtained two steps later in optically active form, establishing the absolute configuration of the natural material as *R*.

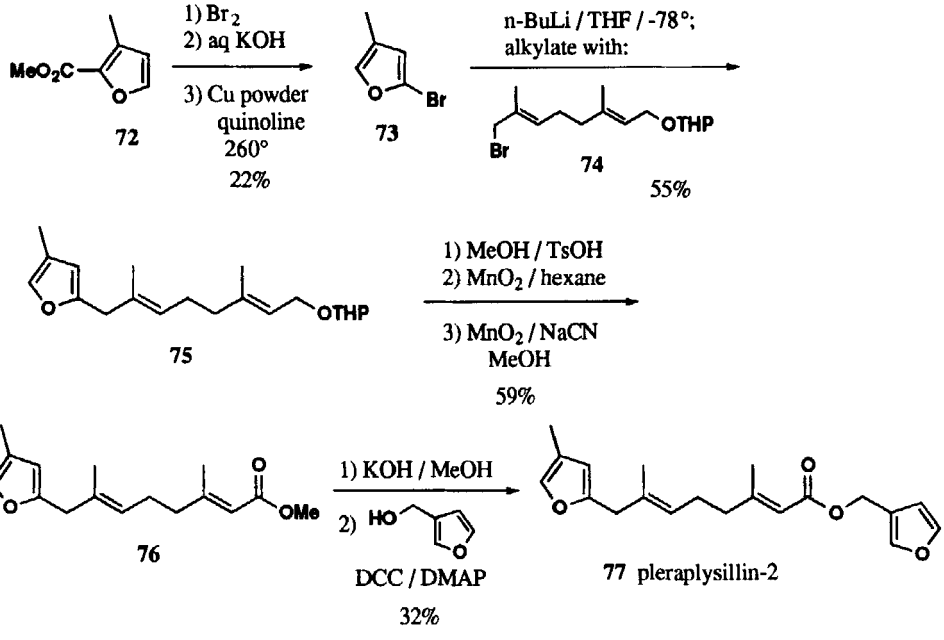
PLERAPLYSILLIN-2

In addition to pleraplysillin-1 *(vide infra)*, the sponge *Pleraplysilla spinifera* gives rise to pleraplysillin-2 (**77**), an esterified sesquiterpene acid.[30] Knight has reported a very direct solution to the 4-methyl-2-substituted furan problem which has resulted in the synthesis of this metabolite (Scheme 19).[31] The previously unknown 2-bromo-4-methylfuran (**73**) was easily produced on the multigram scale from ester **72** by bromination, ester saponification and decarboxylation. Lithium-halogen exchange produced 2-lithio-4-methylfuran which could be alkylated with moderate success with alkyl halides and carbonyl compounds, providing a convenient synthon for the 4-methyl-2-substituted furan system. Alkylation with bromide **74** gave **75** in 55% yield. Conversion to the methyl ester **76** was followed by a two-step transesterification to give the reportedly unstable pleraplysillin-2 (**77**).

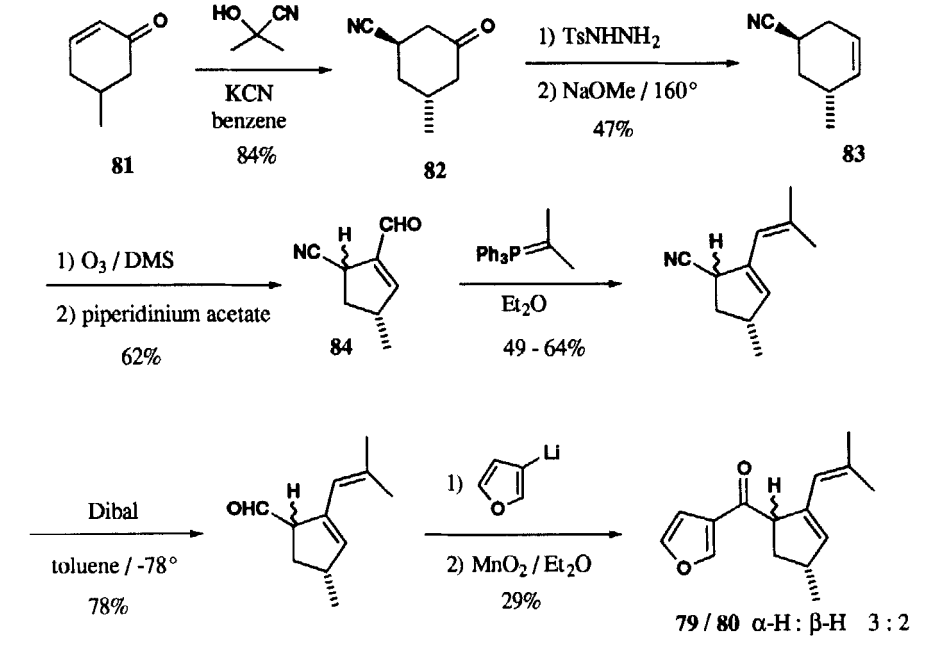
II. COMPOUNDS WITH FURAN AND A FIVE-MEMBERED RING

BICYCLIC EUMORPHA METABOLITES

A number of *Eumorpha* metabolites possess a carbocyclic 5-membered ring in addition to the furan. The two diastereomeric bicyclic metabolites **79** and **80** were also produced by Bohlmann using a single route with a separation at the end (Scheme 20).[32] Conjugate addition of cyanide to enone **81**

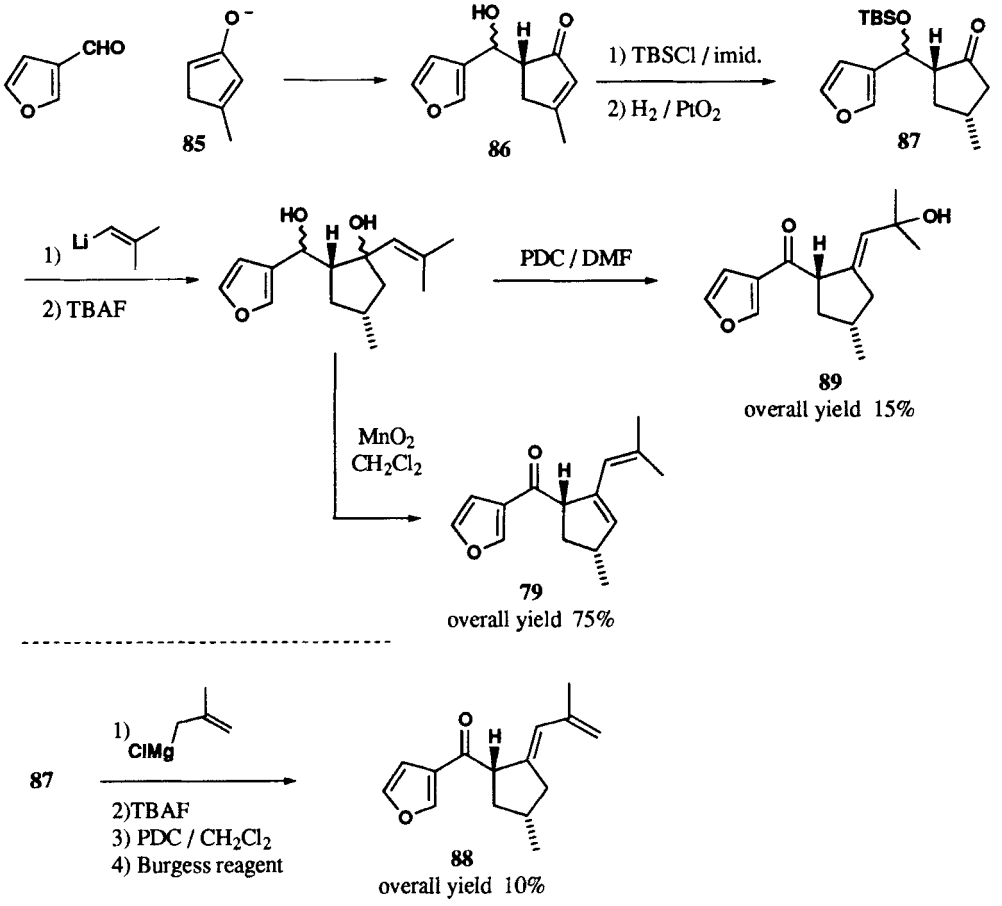


Scheme 19. *Knight Synthesis of Pleraplysillin-2*



Scheme 20. *Bohlmann Synthesis of Eumorpha Metabolites 79 and 80*

gave **82** as a single isomer. Tosylhydrazone formation and decomposition were not carried out in the traditional manner using alkyllithium deprotonation. Instead, heating of the tosylhydrazone of **82** with NaOMe to 160° gave the olefin **83** uncontaminated with the regioisomer, albeit in only 53% yield for this step. The fate of the remainder of the starting material was not addressed. Oxidative cleavage of **83** to the intermediate dialdehyde was followed by intramolecular aldol ring closure and dehydration to give **84**. Unfortunately, this was accompanied by epimerization to an approximately 1:1 diastereomeric mixture. Wittig reaction completed the isobutenyl group while the furan ring was introduced as 3-lithiofuran in an aldehyde addition. MnO_2 oxidation completed the pathway leading to both diastereomers. A stereoselective pathway was reported 6 years later (Scheme 21). The enolate **85** was

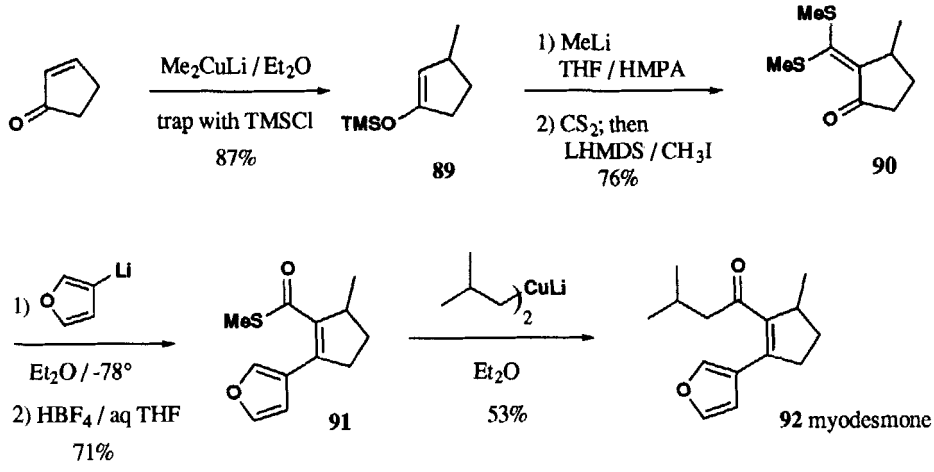


Scheme 21. *Bohlmann Syntheses of Eumorpha Metabolites 79, 88 and 89*

added to 3-furaldehyde to give the adduct **86** as a mixture. Silylation of the alcohol and hydrogenation produced **87** with the *cis* arrangement of the two side-chains off the 5-membered ring. Compound **87** was converted not only to **79** but also to the isomeric metabolite **88** and the alcohol **89** with good overall yields. No yields for the individual steps were reported.

MYODESMONE

Utilizing 1,3-carbonyl transposition methodology, Dieter[33] has assembled myodesmone (**92**), a furanocyclopentene metabolite found in various species of *Myoporum*.[34] Scheme 22 shows the short

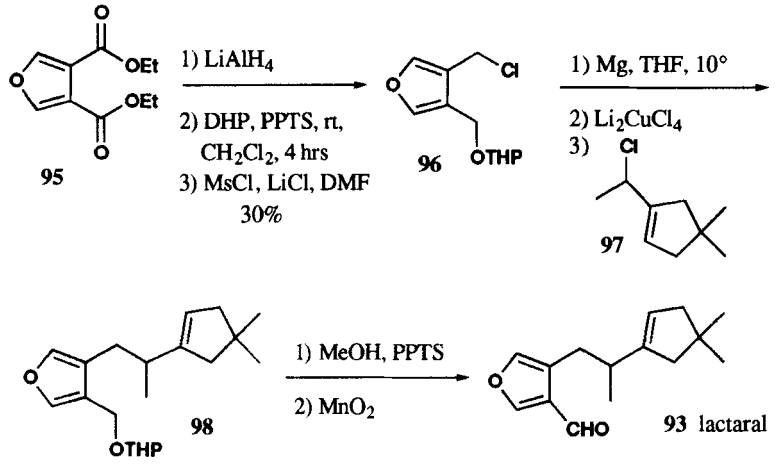


Scheme 22. *Dieter Synthesis of Myodesmone*

route beginning with a cuprate addition-trapping sequence leading to the TMS enol ether **89.** Conversion to the lithium enolate and quenching with CS_2 followed by CH_3I gives the ketene thioacetal **90** in good yield. Addition of 3-furyllithium and acidic rearrangement produces thioester **91** which was converted to racemic **92** on treatment with lithium diisobutylcuprate.

LACTARAL

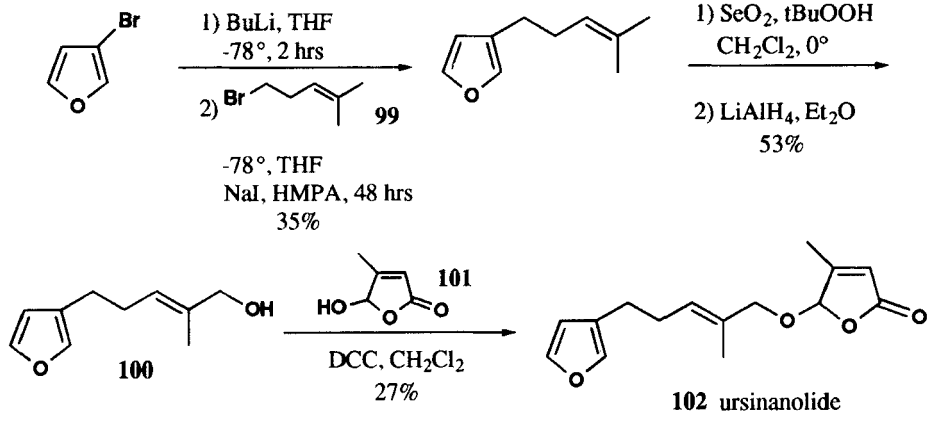
Lactaral (**93**)[35] is a rearranged furanosesquiterpene related to lactarorufin A,[36] a more complex fungal metabolite. Both are found in *Lactarius* sp. The aldehyde reduction product of lactaral (lactarol) was originally synthesized by Thoren[37] and shown to be identical to the alcohol prepared by KBH_4 reduction of lactaral. Lactarol was also shown to be convertible to lactaral by MnO_2 oxidation, thus consummating a formal synthesis of **93**. Lactaral has more recently been synthesized by Tanis[38] by an efficient coupling route (Scheme 23) which is related to the earlier Thoren route. The readily available diester **95** was differentiated *via* a 3 step process to give the synthetically useful 2,3-disubstituted furan **96**. Conversion to the Grignard reagent and then to the cuprate allowed coupling with the allylic halide **97**. Compound **97** was derived from the known corresponding alcohol.[37] Simple manipulation of **98** provided racemic lactaral in a 6 step process.



Scheme 23. *Tanis Lactaral Synthesis*

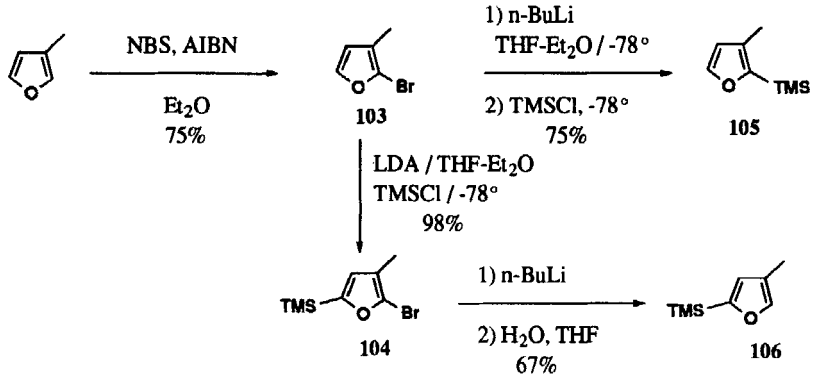
LONGIFOLIN AND URSINANOLIDE

Bornowski[39] has synthesized longifolin[40] (from *Actinodaphne longifolia*) and ursinanolide[41] (from *Ursinia nana*) using basic coupling methodology. Although skeletally distinct, these compounds are considered together here for no other reason than that their syntheses were reported in the same manuscript. Ursinanolide (**102**) was assembled (Scheme 24) by alkylation of 3-furyllithium with



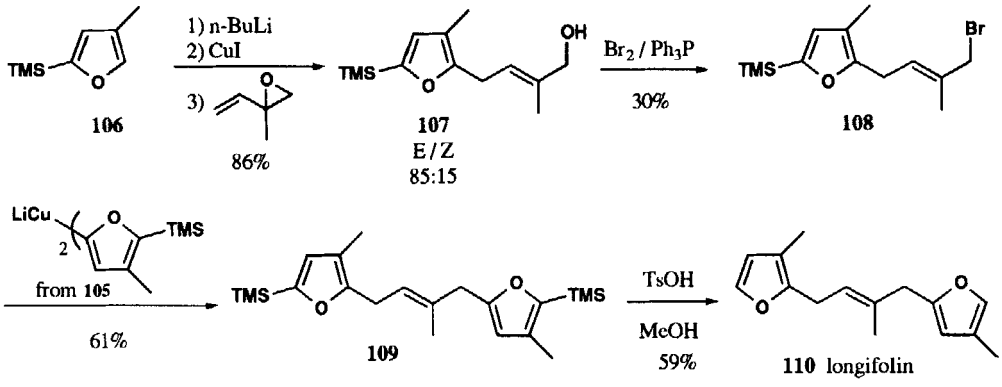
Scheme 24. *Bornowski Synthesis of Ursinanolide*

bromide **99** in moderate yield. Classical selenium dioxide oxidation and reduction gave the *E*-alcohol **100** which was then coupled with the 5-hydroxybutenolide **101** to give ursinanolide **102** in an efficient 4-step synthesis. Longifolin was produced using two silylated methylfurans **105** and **106** as key pieces (Scheme 26). These were produced by bromination of 3-methylfuran to give **103**. Lithium halogen



Scheme 25. *Syntheses of Silylated Methylfurans*

exchange and treatment with TMSCl gave **104** while deprotonation with LDA and quenching with TMSCl gave silane **105**. Lithiation and protonation gave the isomeric furan **106** (Scheme 25). Silylated furans were necessary to ensure production of the regiochemically desired furyllithium reagents by deprotonation. As temporary blocking groups, trialkylsilyl worked quite well here. Silylfuran **106** was deprotonated and converted to the cuprate reagent in the classical manner. Treatment of this reagent with 2-methyl-2-vinyloxirane installed the middle isoprene unit to give **107** as an 85:15 *E/Z*

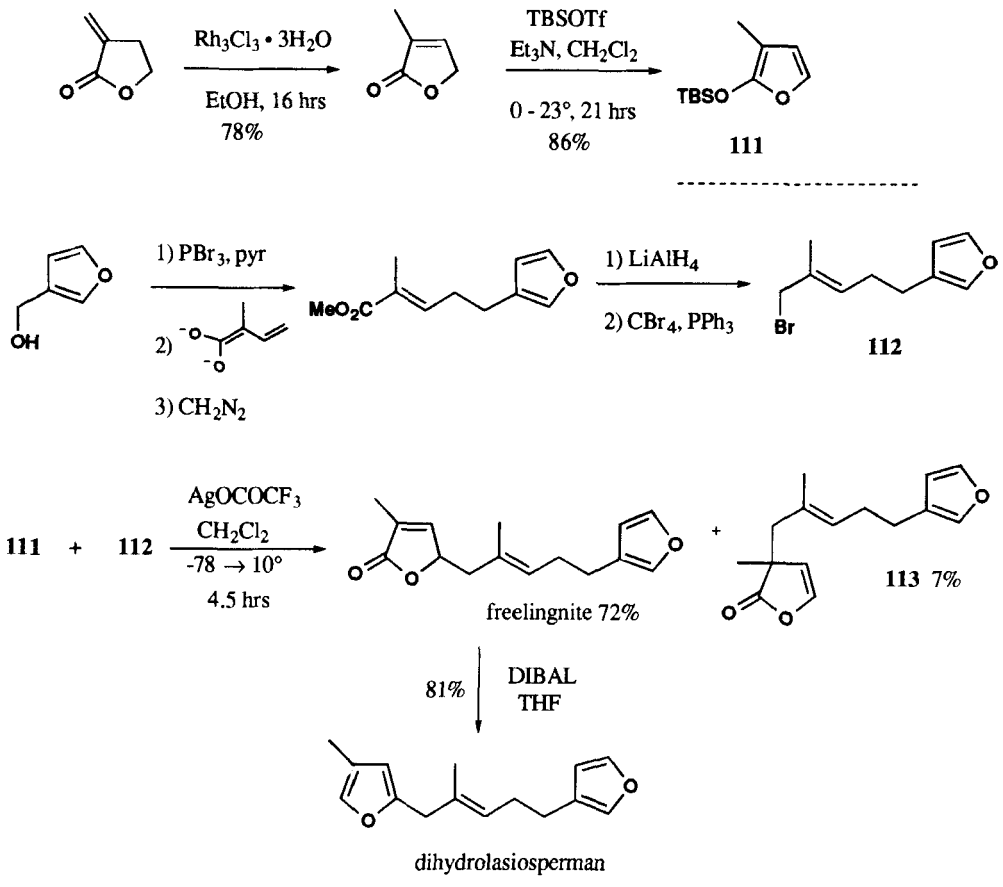


Scheme 26. *Bornowski Synthesis of Longifolin*

mixture. Conversion to the bromide took place in moderate yield to produce **108**. Coupling of this with the cuprate derived from **105** gave **109** in 61% yield. Protodesilylation led to longifolin (**110**). It is ironic that the transformation which appears to be the simplest (**107** → **108**) was the yield-limiting step in the synthesis.

FREELINGNITE AND DIHYDROLASIOSPERMAN

Related to longifolin and ursinanolide are freelingnite[42] and dihydrolasiosperman,[43] which differ from the former pair in the number of carbons between the two furan rings. Jefford used the approach of preparing freelingnite as the precursor to dihydrolasiosperman (Scheme 27).[44] By use

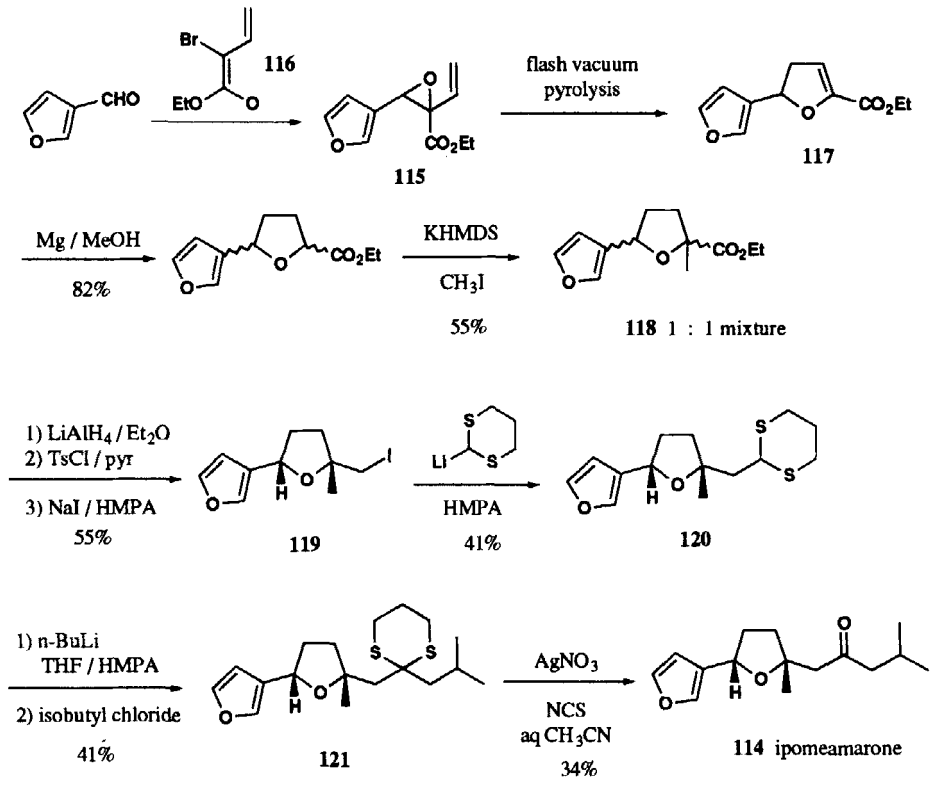


Scheme 27. *Jefford Syntheses of Freelingnite and Dihydrolasiosperman*

of silyloxyfuran alkylation methodology, the TBS ether **111** was combined with the readily available *E*-bromide **112** directly resulting in freelingnite as the major compound formed along with a small amount of the regioisomeric alkylation product **113**. As in many cases, the butenolide (freelingnite) could be converted to the furan (dihydrolasiosperman) with DIBAL.

IPOMEAMARONE

The sweet potato metabolite ipomeamarone (**114**) was identified as one of the first phytoalexins in 1943, isolated by Hiura from *Ipomea batatas*.[45] Prior to 1980, 3 syntheses appeared,[46] although the absolute configuration was worked out in 1983.[47] Hudlicky has developed a route[48] to racemic **114** which does not effectively deal with the relative or absolute stereochemistry problem (Scheme 28). The epoxide mixture **115** was produced by Darzens-like reaction of 3-furaldehyde with the enolate **116**. Pyrolysis of **116** led to the dihydrofuran **117** which was reduced to an inseparable 64:36 mixture of *cis* and *trans* disubstituted tetrahydrofurans. The branching methyl group was installed *via* a classical alkylation giving a 1:1 mixture of isomers **118**. The mixture was reduced to the alcohols, at which point separation was accomplished. The *cis* alcohol was tosylated and



Scheme 28. *Hudlicky Synthesis of Ipomeamarone*

converted to the iodide **119**. Reaction with 2-lithio-1,3-dithiane gave **120** in 41% yield. Attachment of the final four carbons by a second dithiane alkylation also occurred in 41% yield to give **121** which was deprotected to give racemic ipomeamarone.

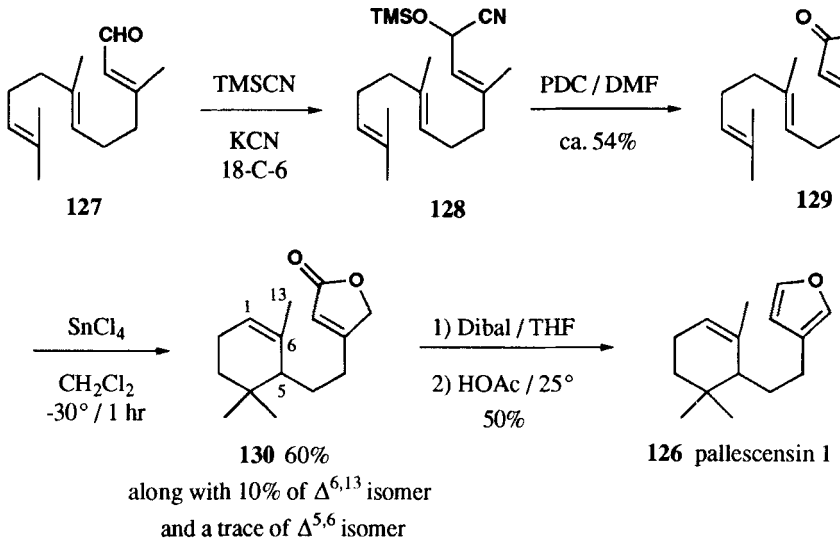
III. COMPOUNDS WITH FURAN AND A SIX-MEMBERED RING

PALLESCENSINS

The pallescensins are a series of related furanosesquiterpenoids isolated primarily from the sponge *Dysidea pallescens*.[49] Bicyclic metabolites such as pallescensin-1, -2 and dihydro-pallescensin-2 will be treated here. The tricyclic metabolites pallescensins A, E, F and G will be discussed in a later section.

PALLESCENSIN-1

Pallescensin-1 (**126**) was first produced during a pallescensin A synthesis of Matsumoto *(vide infra)*. Tius has also prepared this substance as outlined in Scheme 29.[50] A biomimetic cation-olefin cyclization was used to construct the six-membered ring. The O-trimethylsilyl cyanohydrin **128** of aldehyde **127** (available from farnesol) was made with TMSCN. PDC oxidation of this substance in

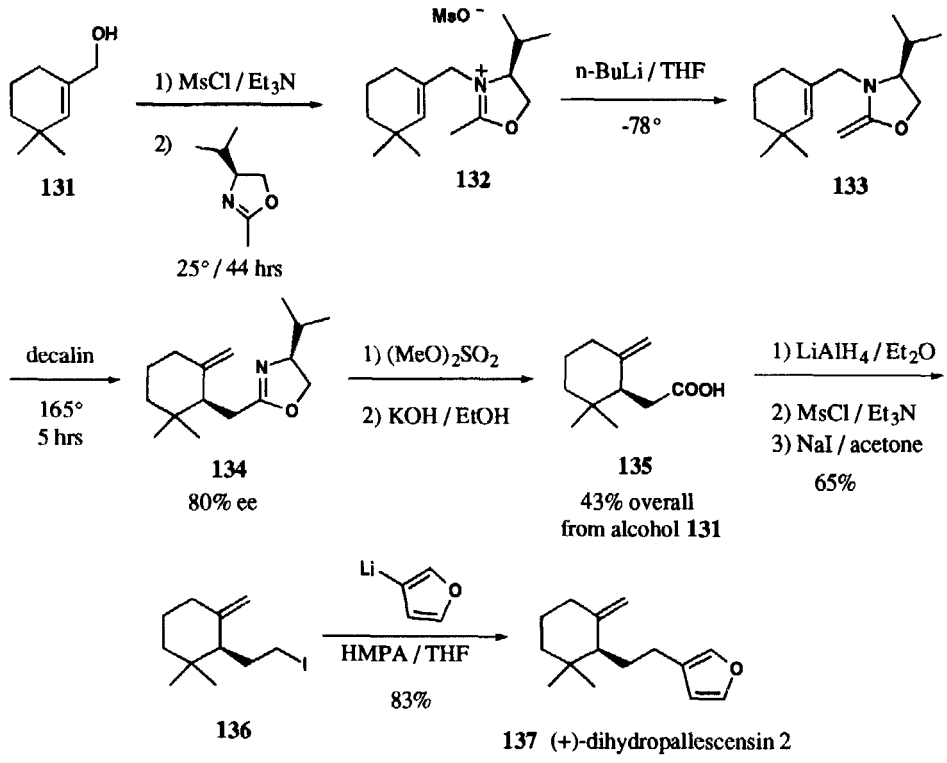


Scheme 29. *Tius Synthesis of Pallescensin 1*

dry DMF afforded the butenolide **129** *via* an allylic oxidation process. Treatment of **129** with $SnCl_4$ produced the cyclized compound **130** in 60% yield along with 10% of the $\Delta^{6,13}$-isomer and a trace of the $\Delta^{5,6}$-isomer. The butenolide was converted to the furan in the now familiar manner to afford pallescensin-1 in a total of 6 steps.

DIHYDROPALLESCENSIN-2 (PENLANPALLESCENSIN)

Dihydropallescensin-2 was first isolated from the nudibranch *Cadlina luteomarginata* by Faulkner[51] in 1982. Three years later the same substance was isolated from *D. fragilis* by Pietra and given the name penlanpallescensin.[52] In the only use of a chiral auxiliary in this series of metabolite syntheses, Kurth has prepared (+)-dihydropallescensin-2 in an enantioselective fashion (Scheme 30).[53] The key step around which the synthesis was built involves an asymmetric aza-Claisen rearrangement. Allylic alcohol **131** (prepared from 2-methylcyclohexanone) was mesylated in 99% yield and then converted to the oxazolinium salt **132**. Titration with *n*-butyllithium gave **133** and heating in decalin gave the rearrangement product **134** in 80% ee. Removal of the chiral auxiliary without lactonization of the free acid was achieved by methylation of the oxazoline and basic hydrolysis affording **135**. Conversion of the acid to the primary iodide **136** occurred *via* a standard sequence. Coupling of the iodide with 3-lithiofuran provided optically-enriched dihydropallescensin-2 (**137**) in 8 steps and 23% overall yield.

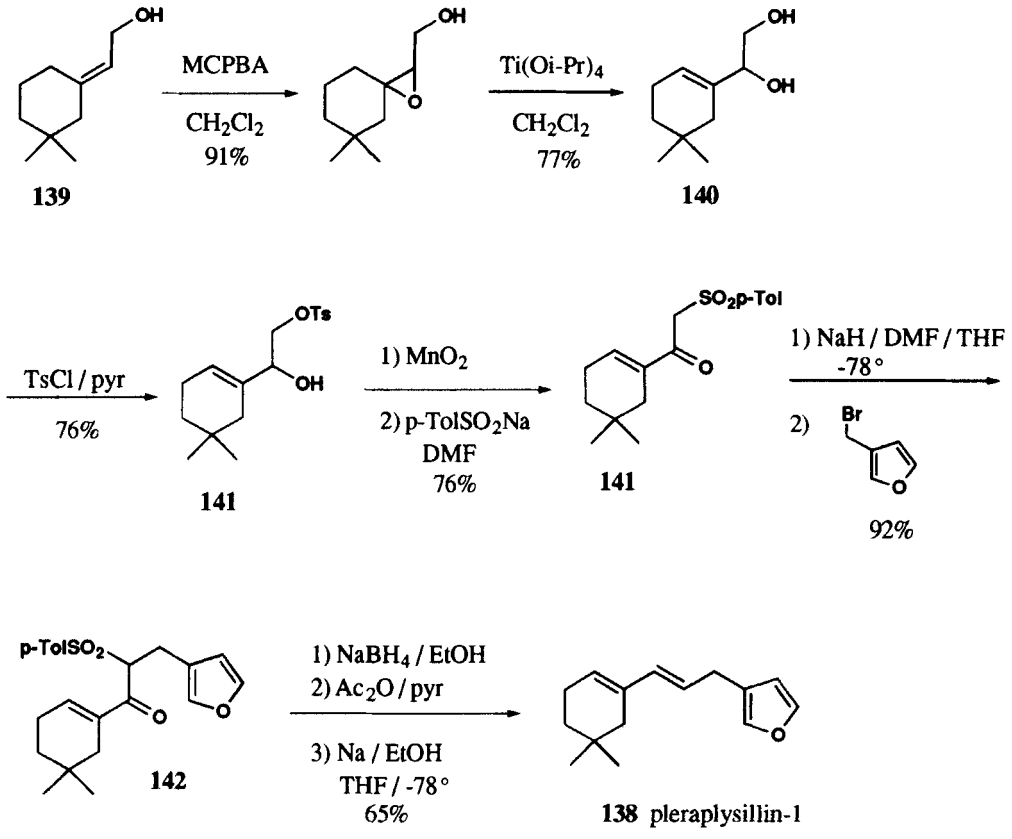


Scheme 30. *Kurth Synthesis of (+)-dihydropallescensin 2 [(+)-Penlanpallescensin]*

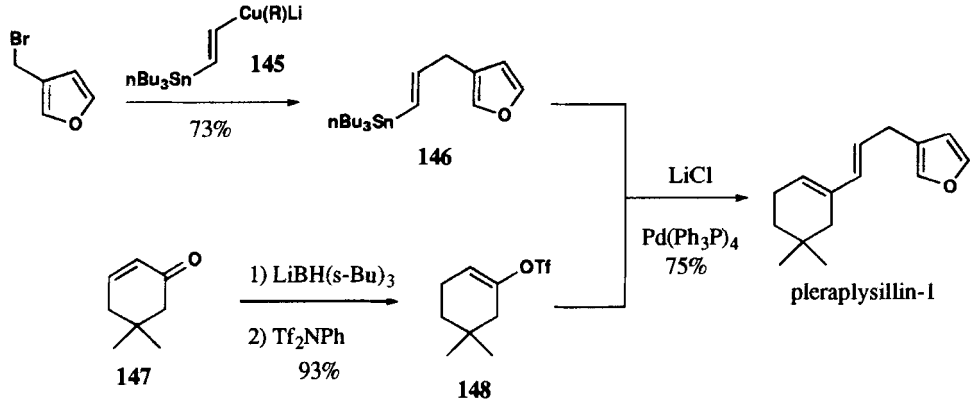
PLERAPLYSILLIN-1

Pleraplysillin-1 (**138**) was isolated from the marine sponge *Pleraplysilla spinifera* in 1972.[54] The structure is simply a 3-furylmethyl extension of the ochtodane[55] monoterpene skeleton. The first synthesis of **138** was developed by Masaki (Scheme 31).[56] The strategy involves the coupling of ochtodane and 3-furylmethyl derivatives to obtain the pleraplysillin-1 framework. Diol **140** is prepared by epoxidation of the known *E*-alcohol **139** followed by Lewis acid-promoted eliminative ring opening. Monotosylation of **140**, allylic oxidation, and displacement of the tosyl group provides the ketosulfone **141**. Coupling of **141** with 3-furylmethyl bromide provides ketone **142**. Carbonyl reduction, acetylation of the resulting alcohol and reductive elimination of the α-acetoxysulfone provides pleraplysillin-1. The metabolite was obtained in 9 steps and 24% overall yield.

Stille[57] developed a very short and efficient synthesis of pleraplysillin-1 based on the palladium-catalyzed coupling of vinyl triflates with organostannanes (Scheme 32). Addition of the lithium *(E)*-vinyltin cuprate **145** to 3-furylmethyl bromide provides the furfuryl vinyltin reagent **146** in 73% yield. Vinyl triflate **148** is prepared as a single regioisomer in 93% yield by conjugate reduction of



Scheme 31. *Masaki Synthesis of Pleraplysillin-1*

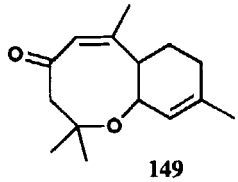


Scheme 32. *Stille Pd-based Synthesis of Pleraplysillin-1*

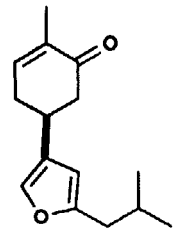
ketone **147** with lithium tri-*sec*-butylborohydride and trapping with N-phenyltriflamide. Palladium-catalyzed coupling of stannane **146** and triflate **148** affords pleraplysillin-1 in 3 steps and 70% yield from 5,5-dimethyl-2-cyclohexen-1-one.

BILOBANONE

The *Gingko biloba* metabolite bilobanone was originally described as structure **149** but the advent of NMR spectroscopy allowed reassignment as **150** in 1968 by Kimura and coworkers.[58] The first synthesis by Buchi[59] appeared a year later and started from (+)-carvone and proceeded in four steps providing optically active bilobanone on the gram scale. This synthesis confirmed the absolute configuration of the natural material as shown in **150**.

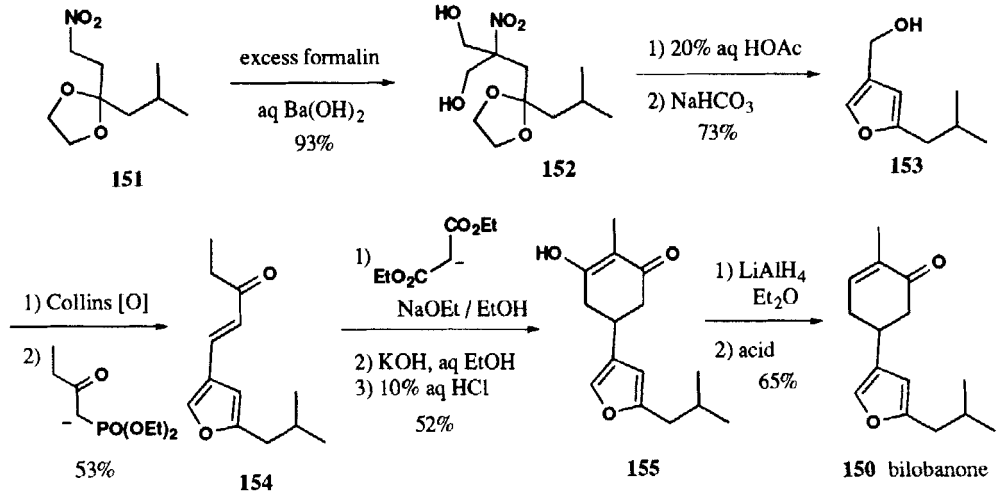


149



150

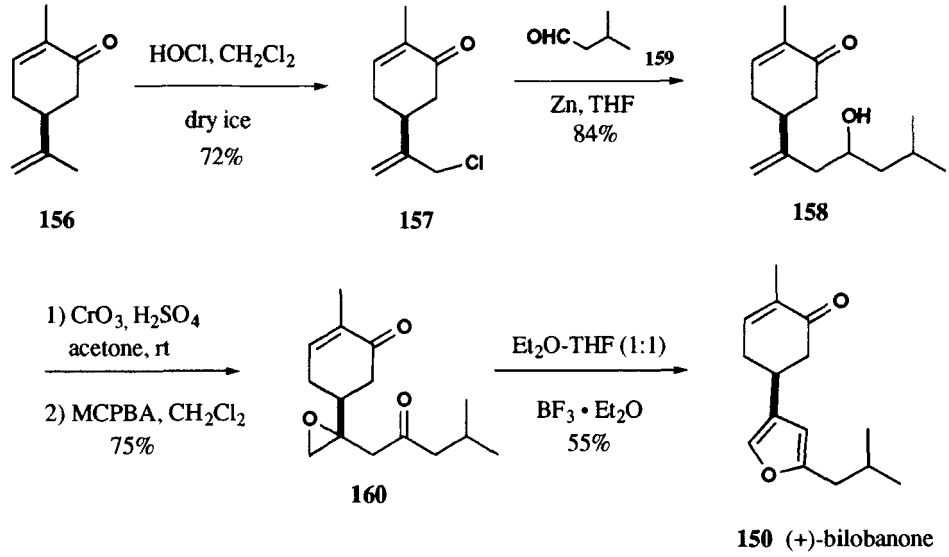
A racemic synthesis was subsequently detailed by Maldonado,[60] relying on the nitroketal **151** for production of the disubstituted furan (Scheme 33). Reaction of **151** with excess formalin in base gave



Scheme 33. *Maldonado Synthesis of Bilobanone*

the diol **152** which was cyclized to the furan **153** by acid treatment followed by neutralization. Collins or MnO_2 oxidation produced the aldehyde which was homologated *via* a Wadsworth-Emmons olefination to **154**. Conjugate addition of malonate, decarboxylation and ring closure produced the enol **155**. Conversion to bilobanone from here was straightforward, resulting in a 12% overall yield from **151**.

Like Buchi, Wolinsky[61] viewed bilobanone as a furan ring-annulated carvone derivative and devised an exceptionally concise and efficient chiral pool approach to this substance (Scheme 34). The key operation is the extension of the isopropenyl group of carvone using a tolerant organozinc

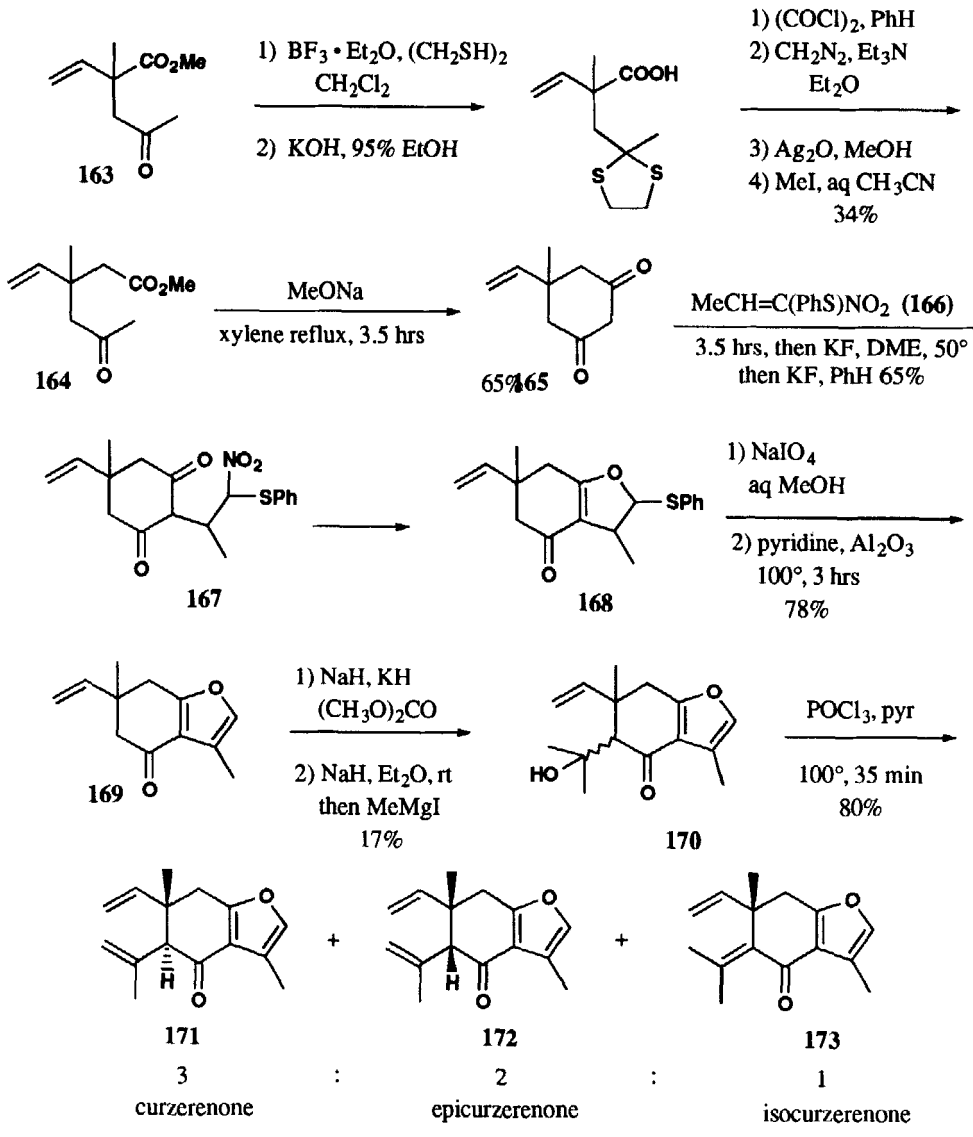


Scheme 34. *Wolinsky Synthesis of (+)-Bilobanone*

intermediate. Reaction of (+)-carvone **156**[62] with HOCl gave the allylic chloride **157**. This was converted to the alcohol **158** in good yield without prior modification of the carbonyl group by treatment with Zn followed by aldehyde **159**. Chromium(VI) oxidation and selective epoxidation gave the mixture of epoxides **160**. Lewis acid-promoted cyclocondensation gave (+)-bilobanone concluding a 5-step process from carvone.

CURZERENONE AND DERIVATIVES

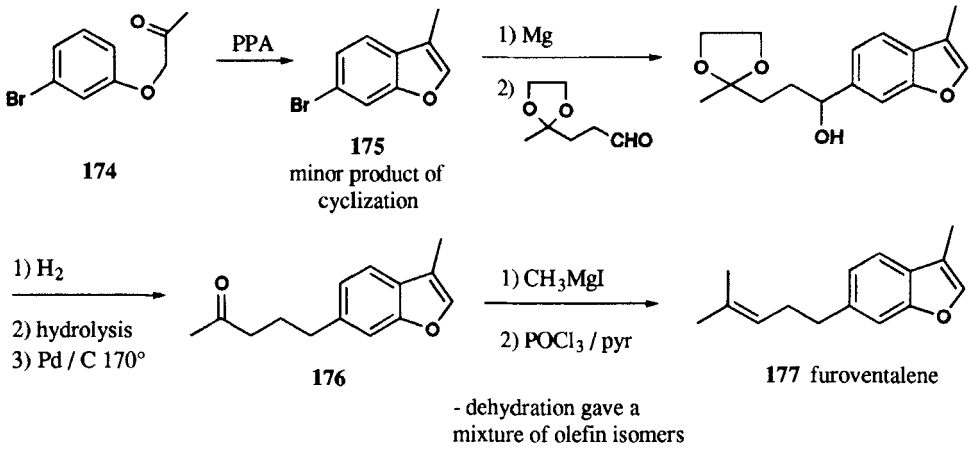
A typical elemane sesquiterpene, curzerenone (**171**)[63] has been produced by Yoshikoshi[64] using furan ring annulation methodology exploited in other syntheses (Scheme 35). The ketoester **163** was converted to the extended ketoester **164** *via* an unremarkable series of manipulations, involving homologation using the Arndt-Eistert process. Treatment of **164** with sodium methoxide promotes Dieckmann-type cyclization to the β-diketone **165** which serves as the substrate for the annulation. Reaction of **165** with the unsaturated nitro compound **166** results in initial conjugate addition to give **167** which undergoes a ring closure to provide the dihydrofuran **168**. Oxidative elimination of PhSOH completes the annulation to furan **169**. Although this looks particularly efficient, compound **169** may not be the optimum intermediate for establishing the *trans* arrangement of the vinyl and isopropenyl groups. A solid stereoelectronic and/or steric bias is not apparent in **169**. The remaining isopropenyl group was nonselectively installed by carbomethoxylation to a mixture of stereoisomers and reaction with CH_3MgI to provide **170**. Elimination of the alcohol gave curzerenone along with the isomeric **172** and **173** in a combined 80% yield.



Scheme 35. *Yoshikoshi Synthesis of Curzerenone*

FUROVENTALENE

The benzofuran sesquiterpene furoventalene (**177**) was isolated from the sea fan *Gorgonia ventalina* by Weinheimer.[65] It possesses an isoprenoid but non-farnesyl skeleton. It was first prepared by Weinheimer in a non-regioselective fashion in order to confirm the proposed structure (Scheme 36). The preparation of the benzofuran system involved an acidic intramolecular cyclization of a ketone onto an aromatic ring followed by elimination. Treatment of bromophenolic ether **174** with polyphosphoric acid produced benzofuran **175** as a minor reaction product. Grignard condensation of **175** with the ethylene ketal of levulinaldehyde followed by hydrogenolysis of the benzylic alcohol

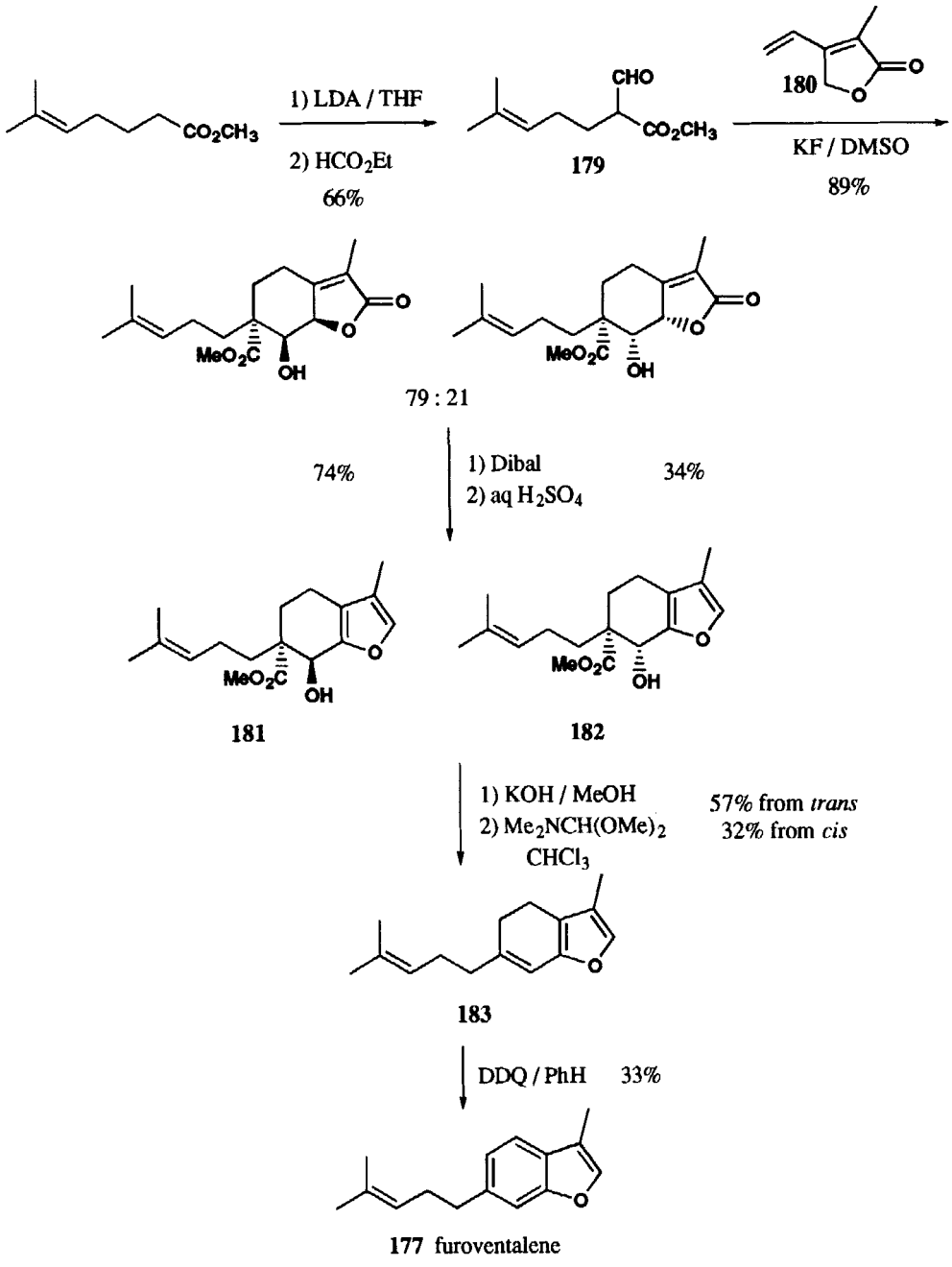


Scheme 36. *Weinheimer Synthesis of Furoventalene*

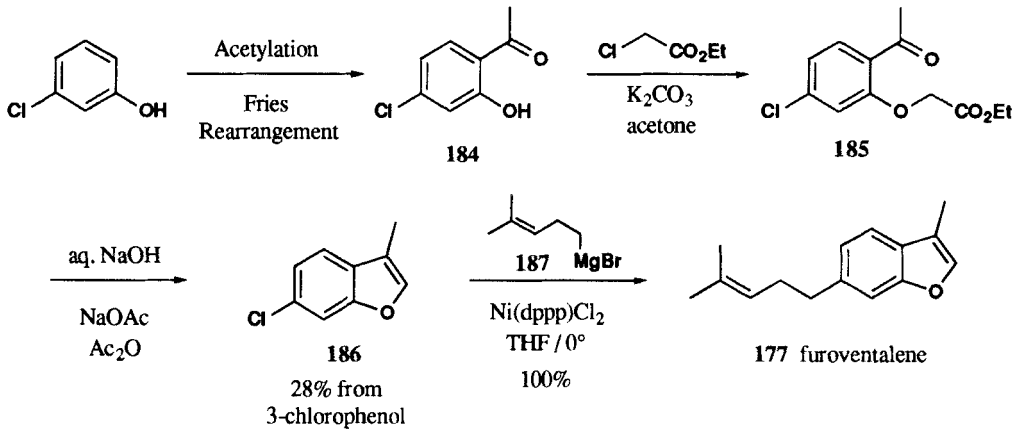
yielded ketone **176** as a mixture with the dihydrofuran. Dehydrogenation of the mixture afforded only **176**. Addition of methylmagnesium iodide and elimination provided furoventalene in a mixture of olefin isomers.

Yoshikoshi[66] developed the synthesis of furoventalene shown in Scheme 37. The general approach involved the annulation reaction of a 1,3-dicarbonyl compound with a β-vinylbutenolide to provide the furoventalene skeleton in one operation. The furan ring was obtained by standard reduction of the butenolide and elimination. In the key transformation, aldehyde **179** was condensed with butenolide **180** by treatment with KF in DMSO to give the annulation product as a mixture of two diastereomers. Separation, followed by DIBAL reduction and acid catalyzed elimination provided furans **181** and **182**. Saponification and elimination by treatment with N,N-dimethylformamide dimethyl acetal produced dihydrobenzofuran **183** which was oxidized with DDQ to give furoventalene. An overall yield of 8% over 7 steps was obtained.

More recently, Bergstrom[67] prepared furoventalene as shown in Scheme 38. The synthesis was initiated by acetylation and Fries rearrangement of 3-chlorophenol to produce the acetophenone derivative **184**. Ketoester **185** was obtained *via* alkylation with ethyl chloroacetate. Saponification of **185** affords an acid, which cyclizes and decarboxylates by heating with fused sodium acetate and acetic anhydride to produce benzofuran **186**. Nickel catalyzed coupling of **186** with Grignard reagent **187** afforded furoventalene in a 6 step process.



Scheme 37. *Yoshikoshi Synthesis of Furoventalene*

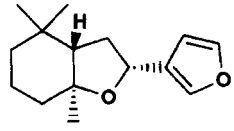


Scheme 38. *Bergstrom Synthesis of Furoventalene*

IV. COMPOUNDS WITH FURAN AND TWO RINGS

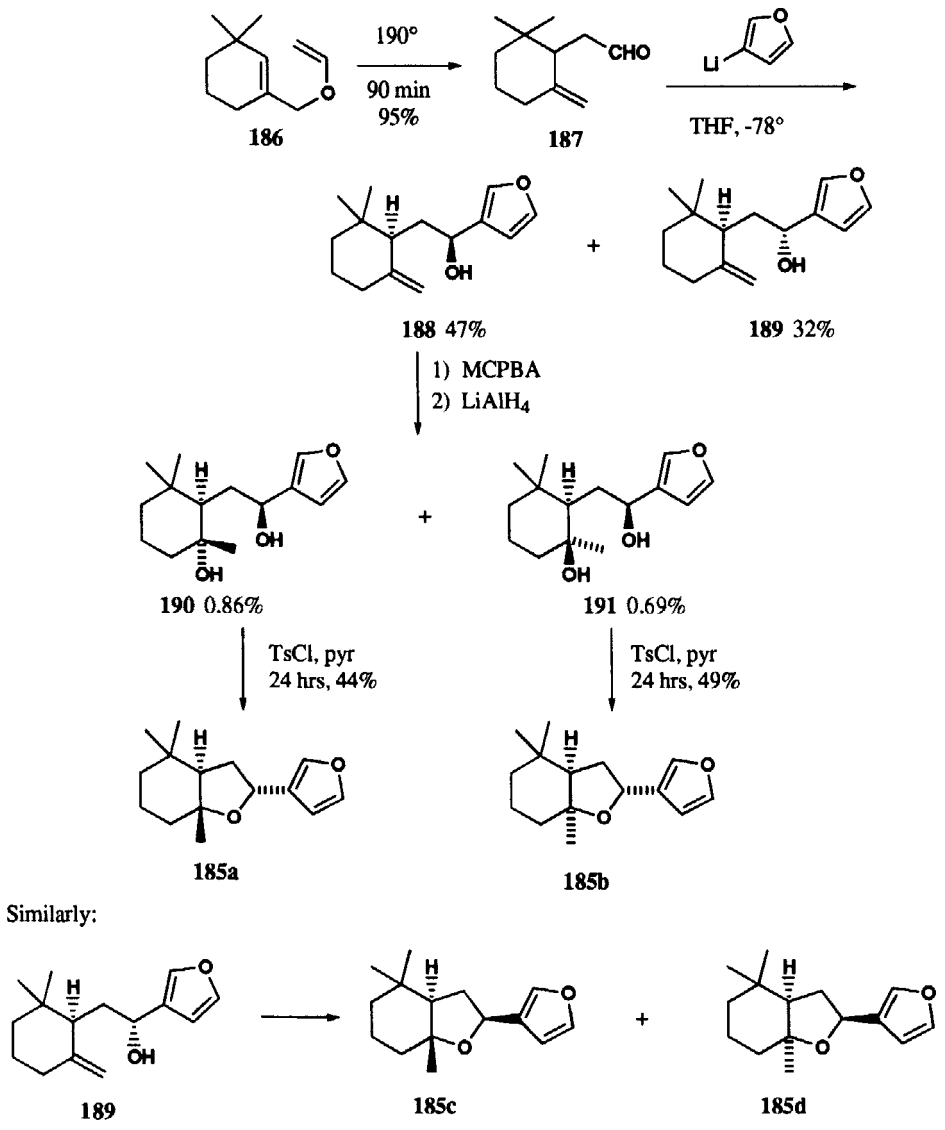
ANCISTROFURAN

The tricyclic metabolite ancistrofuran (**185**), a component of the defensive secretion of the major soldier termite *Ancistrotermes cavithorax*, was described in 1978 by Baker and Evans.[68] At that time, only the gross structure without relative stereochemistry was deduced. A subsequent, nearly



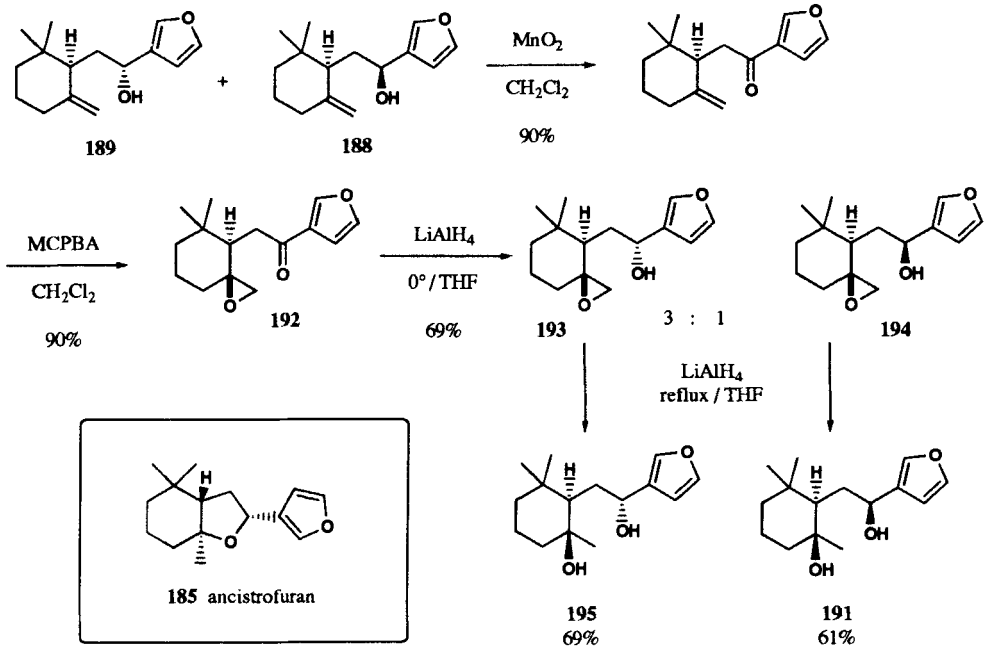
185 ancistrofuran

stereochemically random synthesis, combined with ^{1}H NMR spectroscopy aided in the assignment of the full relative stereochemistry.[69] This communication was followed up in 1985 with full experimental details concerning several pathways to the racemic natural product.[70] The chronologically first synthesis is shown in Scheme 39. In this approach, all four possible stereoisomers of ancistrofuran were prepared. The synthesis began with a Claisen rearrangement of the allyl vinyl ether **186** derived from 2,2-dimethylcyclohexanone. Addition of 3-furyllithium to the resulting aldehyde **187** produced the diastereomeric mixture of alcohols **188** and **189** which were separated. In a very low-yielding reaction, the alcohol **188** was converted to a mixture of diols **190** and **191** by treatment with MCPBA followed by reduction with lithium aluminum hydride. These diols were again separated and each was cyclized to ancistrofuran isomers **185a** and **185b** by treatment with TsCl and pyridine. In a similar manner, the alcohol **189** was transformed to the ancistrofuran isomers **185c** and **185d**. Additional investigations toward improving the yield of the diols involved oxidation of the alcohols **188** and **189** to the corresponding ketone. Treatment of this ketone with MCPBA afforded a single epoxide **192** in

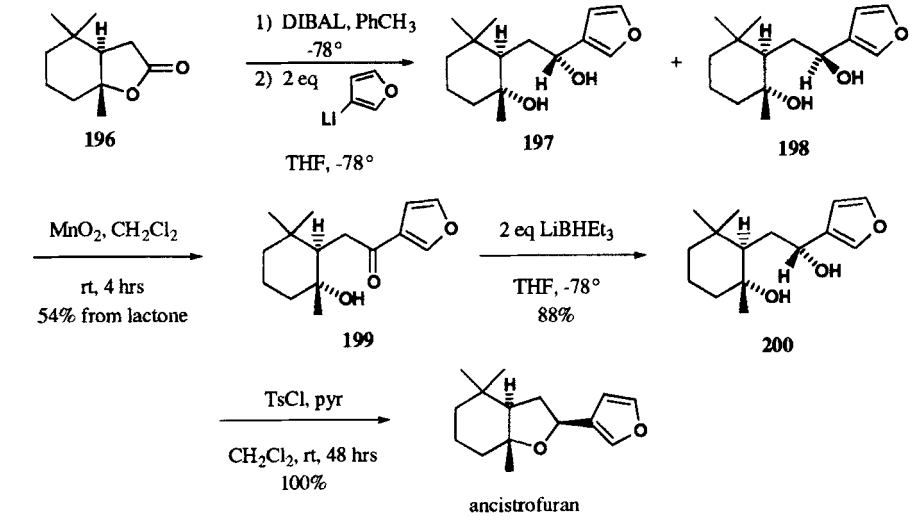


Scheme 39. *Baker Synthesis of Ancistrofuran*

a greatly improved yield. Reduction of the ketone afforded a mixture of alcohols **193** and **194** which were separated and further reduced to the diols **195** and **191** (Scheme 40). A much better approach by the same workers was described in 1984 (Scheme 41).[71] Starting from the lactone **196** which was to serve as an intermediate in many subsequent syntheses, reduction to the lactol and addition of two equivalents of 3-furyllithium yielded the mixture of diols **197** and **198**. The diols were then oxidized with MnO_2 to obtain **199**. Alternatively, **199** could be obtained in a 60% yield by treatment of lactone **196** with one equivalent of 3-furyllithium. Reduction of the ketone to the desired diol **200** could be



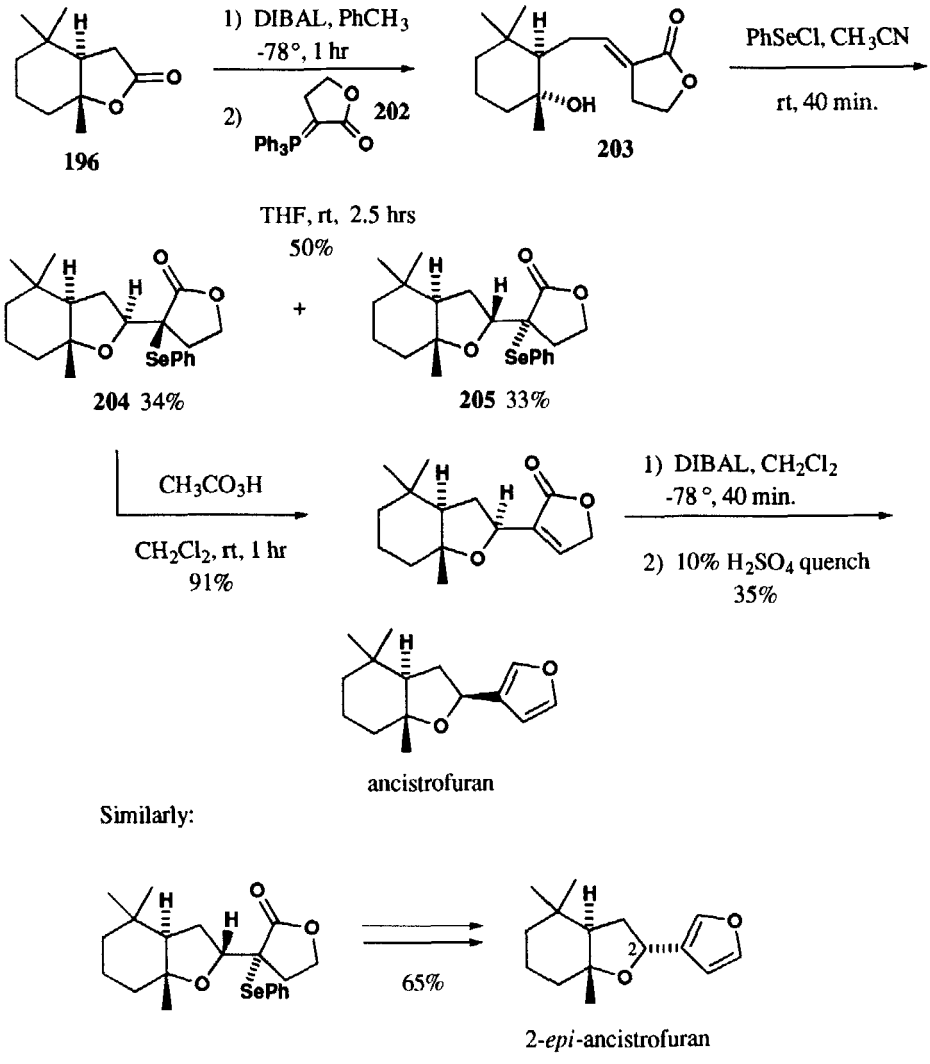
Scheme 40. *Alternate Baker Ancistrofuran Synthesis from Alcohols 188 and 189*



Scheme 41. *Baker 1984 Ancistrofuran Synthesis*

accomplished stereospecifically using $LiBHEt_3$. Other reducing agents did not exhibit this same degree of selectivity. Chelation of the boron reducing agent to both the ketone and the ring hydroxyl was proposed to explain this selectivity. The diol **200** was then treated with TsCl to effect cyclization to racemic ancistrofuran. The overall yield of this very efficient synthesis was 53%.

Since the original syntheses, a variety of successful approaches have appeared, the majority of which produce racemic product. In 1981, Hoye reported a synthesis of both ancistrofuran and its C-2 epimer (Scheme 42).[72] This was presented as part of a general study of cyclic ether formation. The

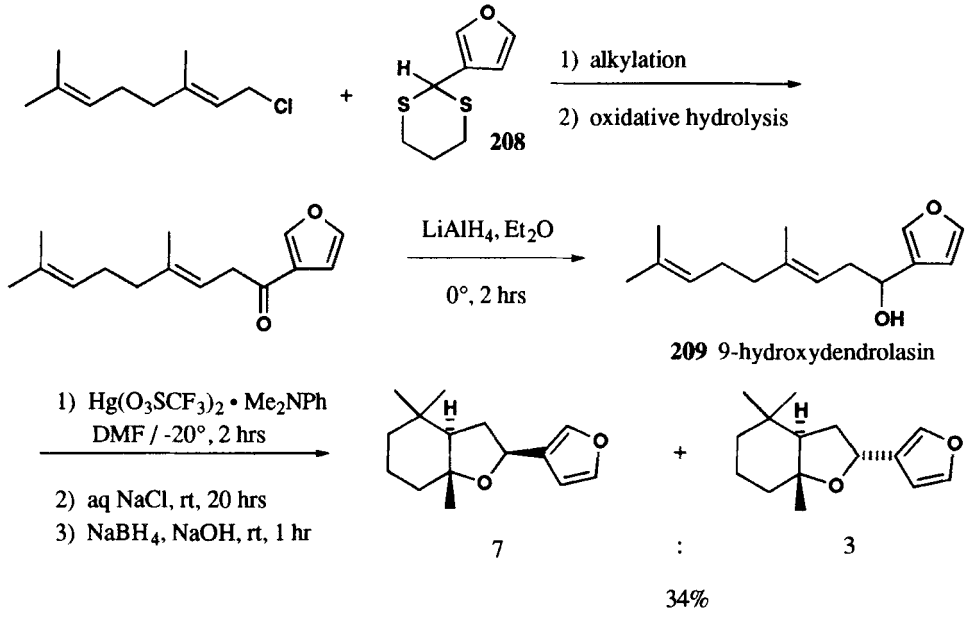


Scheme 42. *Hoye Ancistrofuran Synthesis*

starting material was the previously seen fused lactone **196** which was prepared by a mercuric ion-promoted cyclization of homogeranic acid. The lactone was reduced with DIBAL and the resulting lactol underwent a Wittig reaction with the lactonic phosporane **202** to give **203**. Electrophilic cyclization with PhSeCl resulted in a 1:1 mixture of the diastereomeric lactones **204** and **205** which were readily separable. A series of routine transformations to convert **204** to the furan completed the

synthesis of racemic ancistrofuran in a 5% overall yield from **196**. In the same manner, lactone **205** was converted to the C-2 epimer of ancistrofuran.

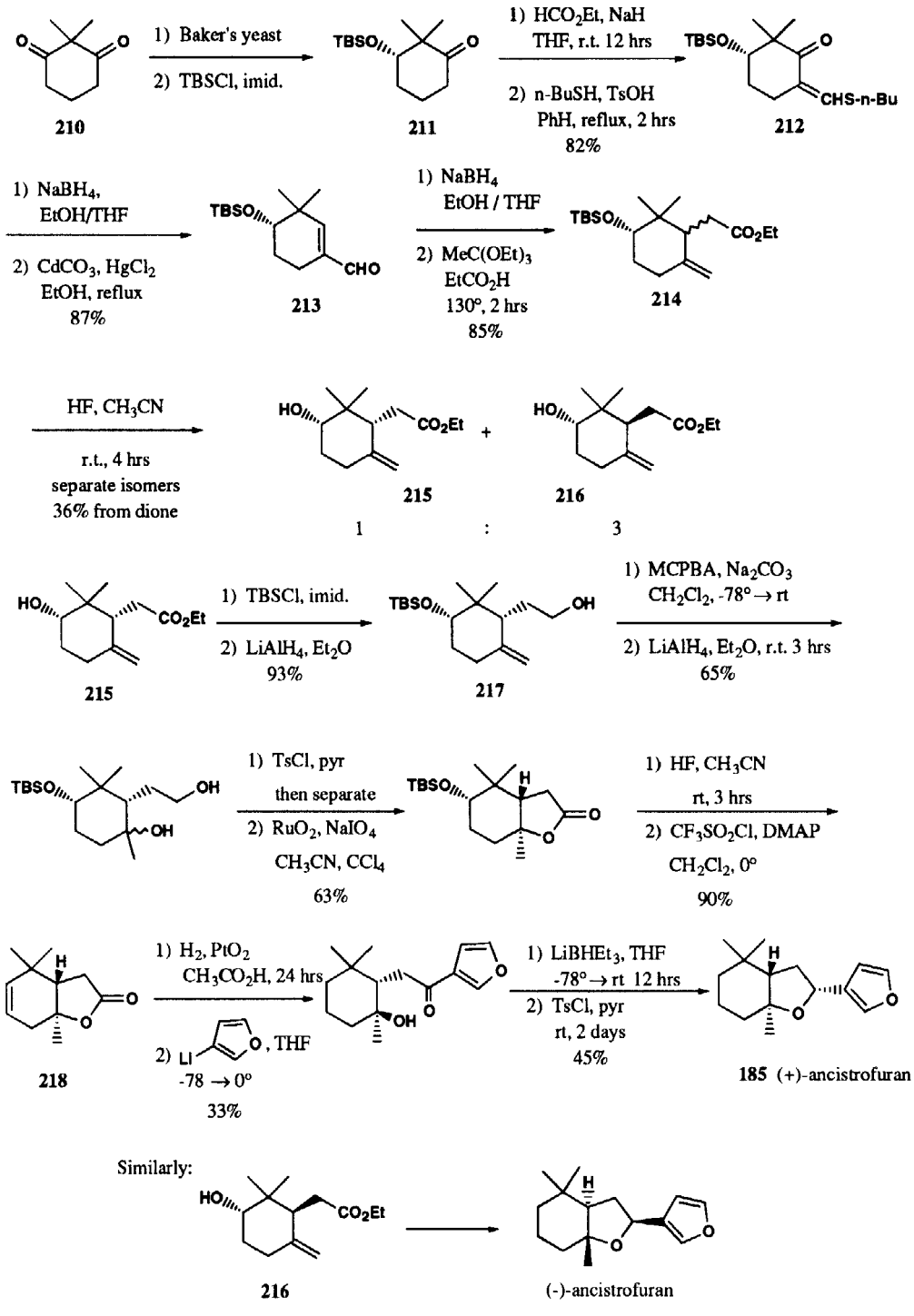
A synthesis which employed a cationic polyene cyclization was reported by Saito in 1986 (Scheme 43).[73] The cyclization precursor was 9-hydroxydendrolasin (**209**), prepared by alkylation of



Scheme 43. *Saito Synthesis of Ancistrofuran*

the dithiane **208** with geranyl chloride. The resulting dithiane was hydrolyzed to the ketone which was reduced with lithium aluminum hydride. Cyclization was effected with an N,N-dimethylaniline complex of mercuric triflate to produce a 7:3 mixture of ancistrofuran and the C-2 epimer, respectively.

In 1990, Mori reported a synthesis of both enantiomers of ancistrofuran (Scheme 44).[74] Reduction of the dione **210** with baker's yeast, followed by protection of the resulting alcohol provided the enantiomerically pure **211** which was converted to the *n*-butylthiomethylene ketone **212** by formylation and treatment with *n*-BuSH. Reduction of the ketone and deprotection with mercuric chloride and cadmium carbonate revealed the aldehyde **213**. Another reduction was followed by Claisen rearrangement to the ester **214**. Removal of the TBS protecting group afforded a 1:3 mixture of the diastereomeric alcohols **215** and **216** which were separated. Each alcohol was then taken on individually through a sequence of steps to the final products. Reprotection of the secondary alcohol and reduction of the ester provided the alcohol **217**. Treatment with MCPBA resulted in a mixture of epoxide isomers which were reduced with $LiAlH_4$ to form a mixture of diols. Treatment with TsCl gave rise to cyclic ethers, which were separated and the appropriate isomer was oxidized to the lactone with RuO_4. The undesired alcohol functionality was removed *via* a standard sequence going

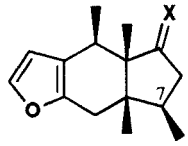


Scheme 44. *Mori Ancistrofuran Synthesis*

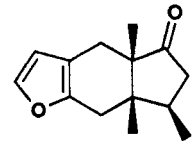
through the olefinic lactone **218**. Hydrogenation then furnished the lactone **196**, the same starting lactone used in previous syntheses, in an enantiomerically pure form. As previously reported by Baker, addition of 3-furyllithium, reduction with $LiBHEt_3$ and tosylation completed the synthesis of (+)-ancistrofuran. Similarly, (-)-ancistrofuran was prepared from the diastereomeric alcohol **216**.

PINGUISANES

Pinguisone[75] (**220**) and deoxypinguisone[76] (**221**) are linear tricyclic metabolites isolated from the liverworts *Aneura pinguis* and *Ptilidium ciliare* respectively. Although possessing moderate antifeedant and antifungal activity,[77] these compounds have attracted very little attention. Their most synthetically challenging feature is four methyl groups on contiguous carbons all extending from one



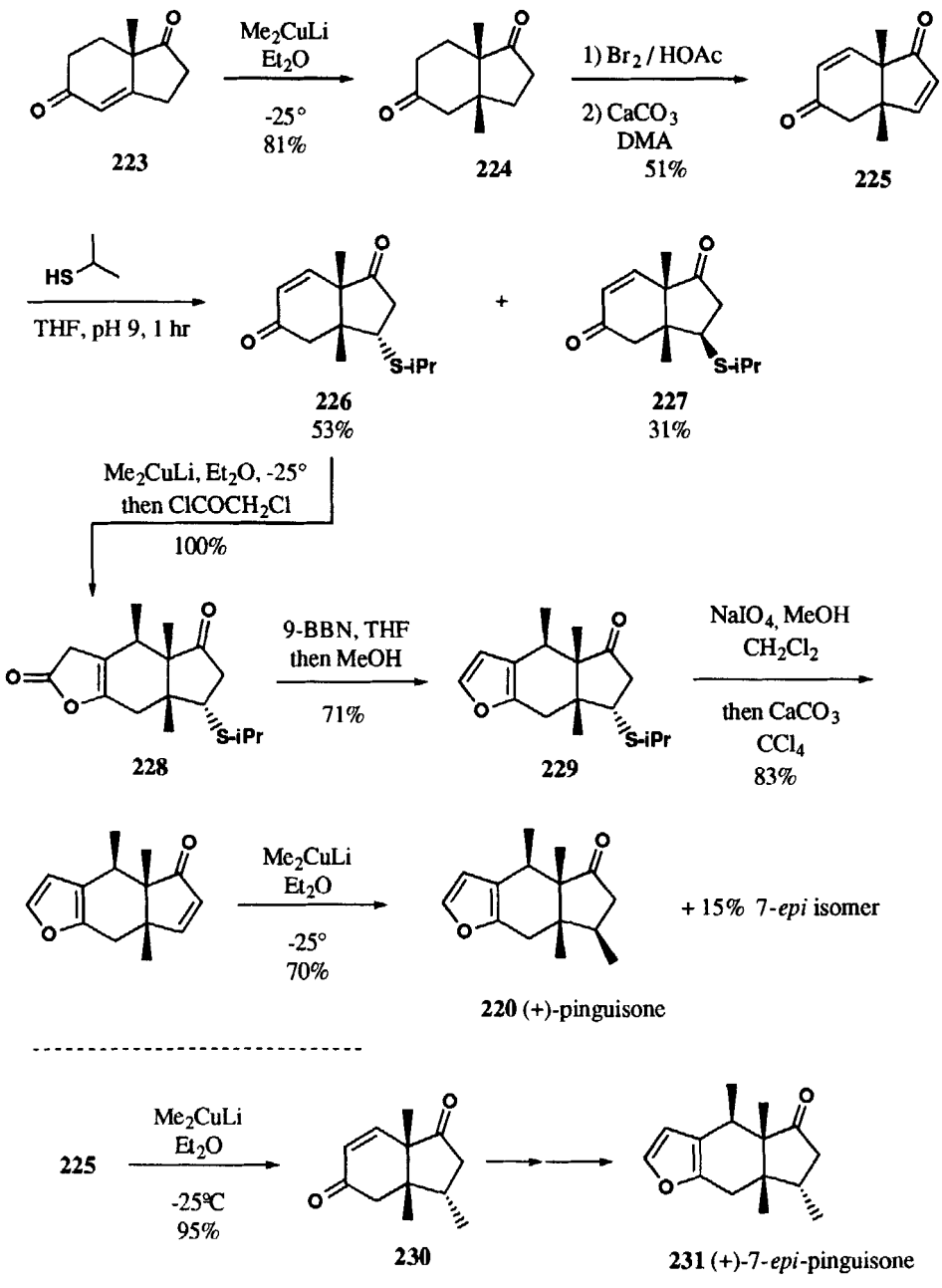
220 X = O pinguisone
221 X = H2 deoxypinguisone



222 norpinguisone

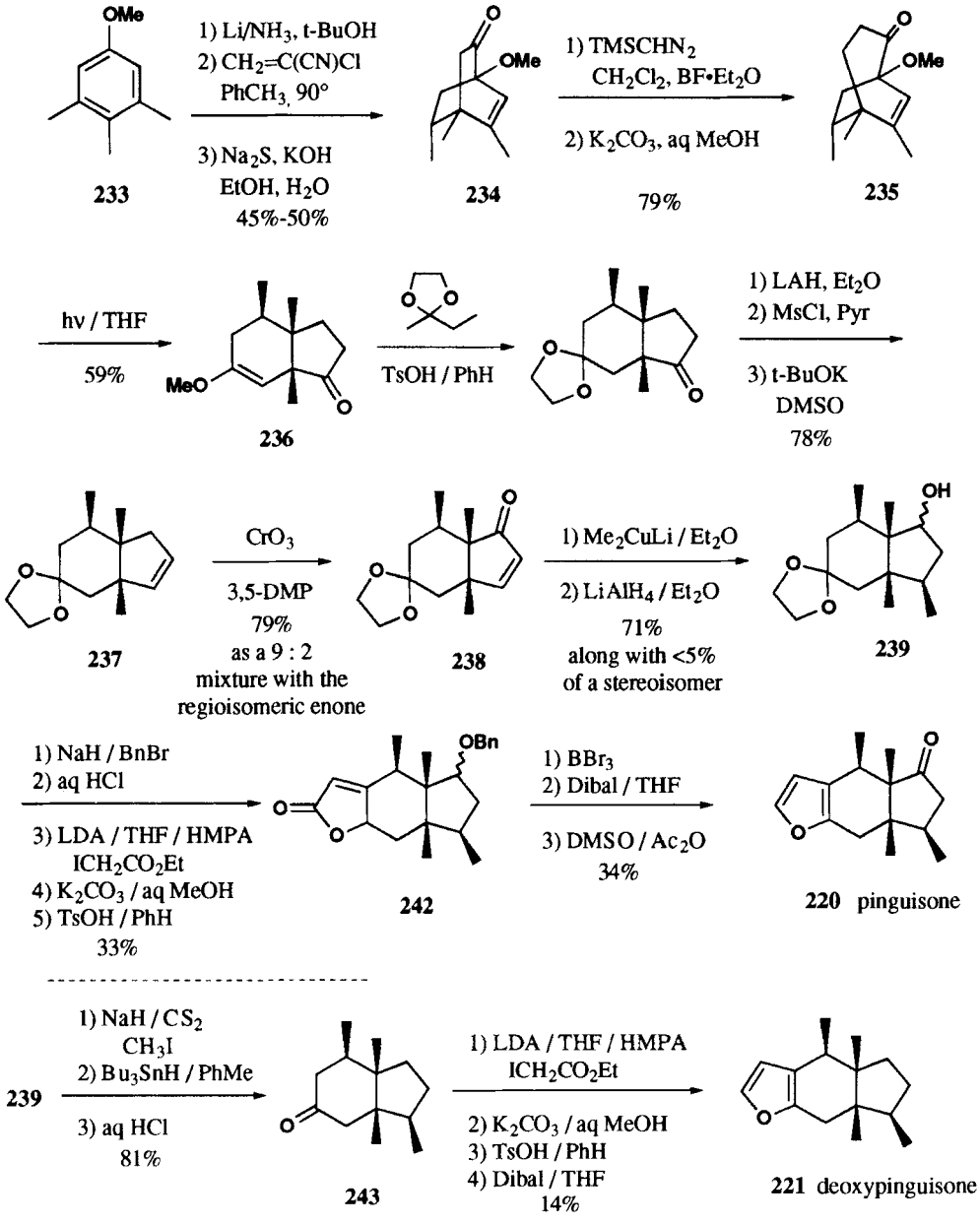
face of a bicyclo[4.3.0]nonane subfragment. One might expect this crowded arrangement to offer some stimulus to the synthetic chemistry community, but apparently the lack of truly potent biological activity is a barrier to attracting broad interest. In any case, successful efforts have been reported in the syntheses of **220** - **222** and (+)-7-*epi*-pinguisone.

In a general approach to the pinguisane skeleton, Jommi has reported the preparation of both (+)-pinguisone and its 7-*epi* isomer (Scheme 45).[78] The general strategy was to add the methyl groups in a piecemeal fashion to a bicyclo[4.3.0]nonane, using the biased shape of the substrate to establish the all *cis* arrangement of the four methyl groups. Using the optically pure Hajos-Parrish dione **223**[79] as the source of the bicyclo[4.3.0]nonane ring system, addition of lithium dimethylcuprate established the *cis* relationship between the two rings resulting in **224**. A bis-bromination-dehydrobromination sequence led to bis-enone **225**, preparing the two rings for further functionalization. Conjugate addition of isopropanethiol gave the two stereoisomers **226** and **227** in ca. 5:3 ratio. No addition to the 6-membered ring enone was recorded. Addition of Me_2CuLi to the major isomer followed by trapping of the resultant enolate with chloroacetyl chloride provided the lactone **228** in quantitative yield, establishing a third stereocenter and the oxygen heterocyclic ring in a single efficient process. Classical reduction and dehydration gave the furan **229**. Installation of the final methyl group at C7 was accomplished again *via* a cuprate conjugate addition providing (+)-pinguisone in 70% yield along 15% of the 7-*epi* isomer **227**. It is tempting to assign the origin of the stereoselectivity of the cuprate addition to **226** to the presence of a bulky isopropanethiol group on the bottom face of the ring system. In the absence of data concerning cuprate addition to the isomeric compound **227**, this is a tenuous rationale. Note, however, that cuprate addition to **225** gives the C7 epimer **230**, consistent with this hypothesis. Compound **230** was carried on to (+)-7-*epi*-pinguisone (**231**) *via* an analogous series of reactions.



Scheme 45. *Jommi Syntheses of (+)-Pinguisone and (+)-7-epi-Pinguisone*

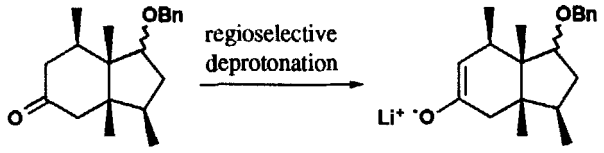
Uyehara has described routes to both pinguisone and deoxypinguisone using a photochemical rearrangement as strategy-level process[80] (Scheme 46). Birch reduction of **233** was followed by Diels-Alder cycloaddition of α-chloroacrylonitrile carried out at 90° to promote olefin conjugation. Treatment with sodium sulfide in aqueous base fulfilled the destiny of the ketene equivalent and resulted in



Scheme 46. *Uyehara Syntheses of Pinguisone and Deoxypinguisone*

the trimethylated bicyclo[2.2.2]octenone **234**. Ring expansion using trimethylsilyldiazomethane gave ketone **235**. Allylic rearrangement from the bridged bicyclic to the fused bicyclic isomer **236** was accomplished by irradiation in THF providing **236** in 59% yield. This rearrangement, along with the preceding [4+2] cycloaddition step, allowed placement of 3 of the four *cis*-oriented methyl groups on

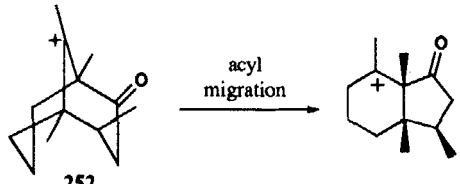
a bicyclo[4.4.0]nonane ring intermediate. Conversion of the enol ether to the dioxolane and manipulation of the remaining ketone gave olefin **237**. Allylic oxidation with CrO_3 / 3,5-dimethylpyrazole gave primarily the enone **238** along with a small amount of the allylically rearranged isomer. Dimethylcuprate addition to **238** occurred predominantly from the top face giving **239** after a nonselective $LiAlH_4$ reduction. This result contrasts with the methylation of **225** → **230** in the Jommi synthesis (Scheme 45). Conversion to the benzyl ether and deprotection gave the intermediate ketone **240** (below) which underwent deprotonation and alkylation regioselectively to give the correctly fused



240 **241**

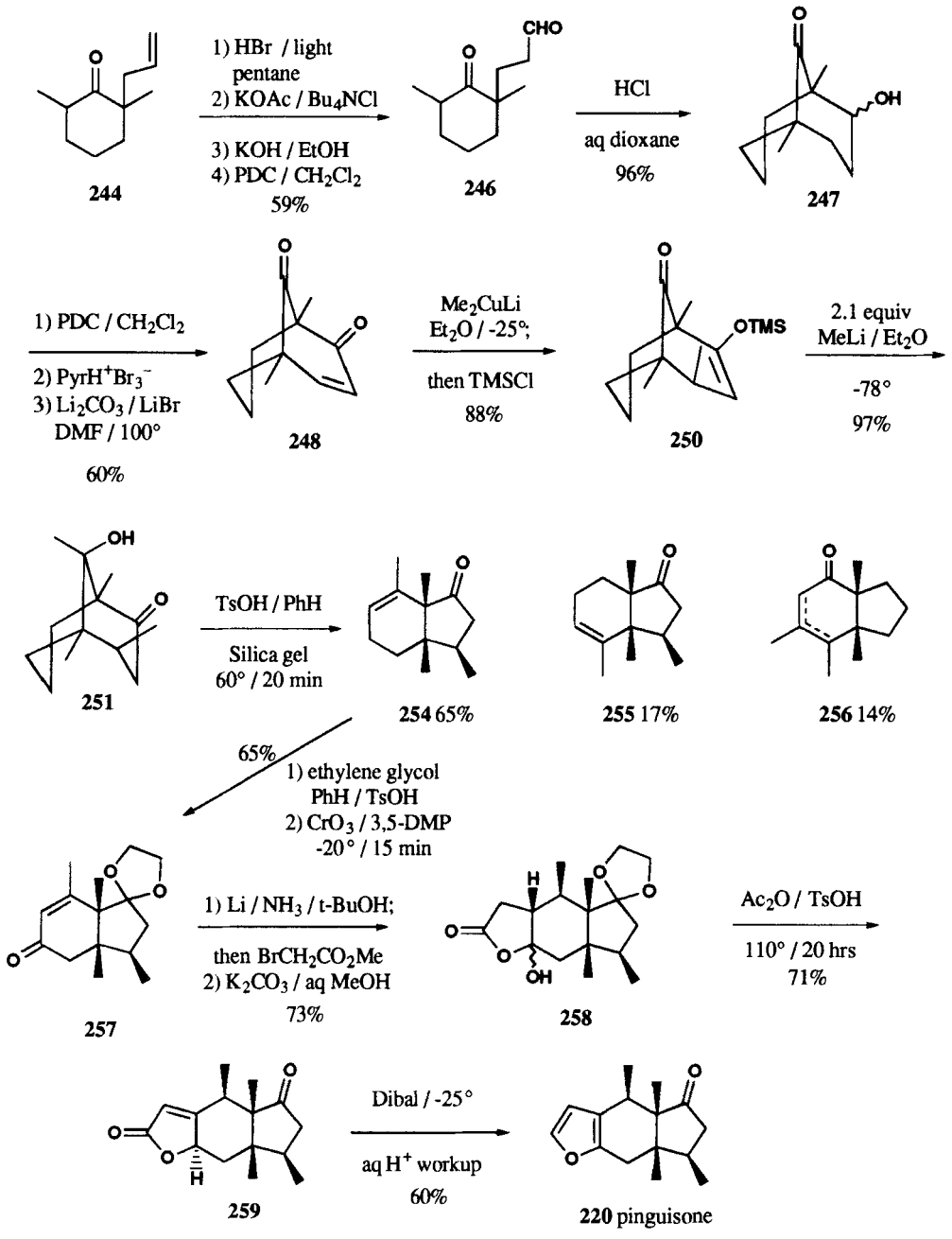
lactone **242** after two more steps in overall 33% yield from **239**. A standard sequence was used to convert **239** to racemic pinguisone, capping a 21 step route. Racemic deoxypinguisone was produced from intermediate **239**, with radical deoxygenation of the C5 alcohol producing **243**. An analogous furan ring annulation gave **221** in 11% overall yield from **239**.

Gambacorta has reported a synthesis of pinguisone using a very similar approach, also involving a bridged bicyclic to fused bicyclic rearrangement process (Scheme 47).[81] The allylated cyclohexanone **244** was converted to the aldehyde **246** which underwent intramolecular aldol reaction giving the alcohol **247** as an inconsequential mixture of stereoisomers. Routine transformations led to enone **248**. The third of the four methyl groups was stereocorrectly installed by lithium dimethylcuprate addition to **248**, trapping the adduct as its TMS enol ether **250**. Treatment with slightly more than 2 equiv of MeLi led to addition of the last methyl group to give **251**, with a convenient, concomitant desilylation providing the substrate for the key rearrangement. Treatment of **251** with acidic silica gel gave rise to 3 products, the major of which arose from the migration of the acyl carbon (**252** → **253**, below) giving **254** in 65% yield. The other 2 isomers obtained were, unfortunately,



252 **253**

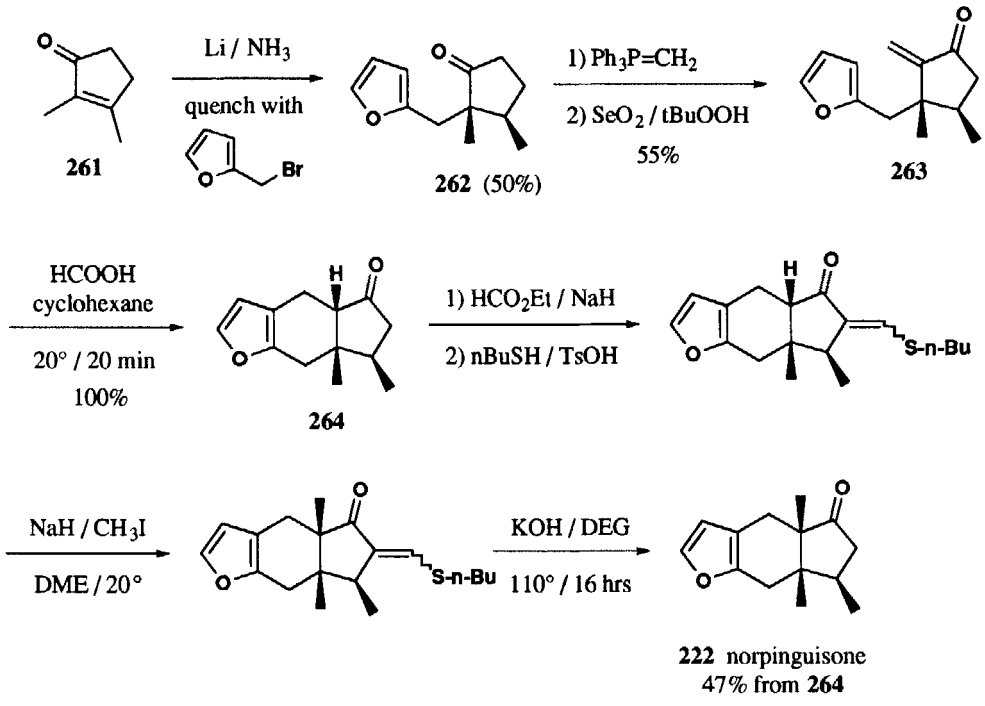
not useful toward the synthetic goal. Carbonyl protection and allylic oxidation proceeded regioselectively providing the ketone **257** in 82% yield (in the oxidation step) along with 8% of the aldehyde derived by methyl group oxidation. From this point the synthesis paralleled that of Uyehara. A Birch reduction-alkylation sequence adds the final two carbons eventually giving lactone **258**. It was found



Scheme 47. *Gambacorta Synthesis of Pinguisone*

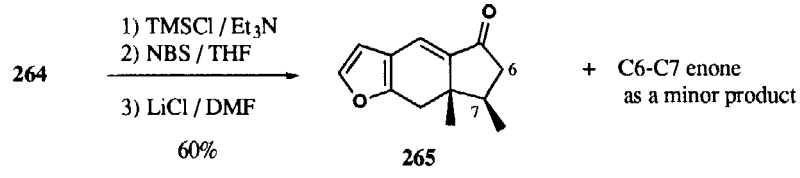
that dehydration and isomerization of the resulting olefin could be accomplished in one step by treatment of **258** with acetic anhydride and TsOH at 110° resulting in the penultimate compound **259** which was taken on to racemic pinguisone *via* the usual method.

Although not resulting in a naturally occurring substance, the synthesis of norpinguisone by Mateos (Scheme 48) is noteworthy for its convergency, resulting in a very efficient strategy to



Scheme 48. *Mateos Synthesis of Norpinguisone*

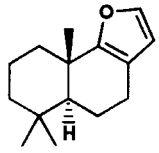
produce the general pinguisane ring system.[82] The cyclopentenone **261** was Birch reduced to the enolate and alkylated *in situ* with the labile 2-furyl bromide resulting in a 4:1 mixture of the desired cyclopentanone **262** along with the minor diastereomer in combined 63% yield. A mixture of difuryl ketones was also obtained in 10% yield. This accounted for a 50% yield of desired product. Wittig methylenation and allylic oxidation led to enone **263**. Treatment of **263** with anhydrous formic acid in cyclohexane at room temperature promoted cyclization to the less strained *cis*-fused tricycle **264**. Regioselective methylation at the ring fusion required the use of the classical *n*-butylthiomethylene blocking group providing norpinguisone **222** in 8 steps from **261** in 13% overall yield. The conversion



of ketone **264** to enone **265** was reported in this article but no subsequent chemistry of **265** was described. It is not hard to imagine what transformations of **265** were attempted, however.

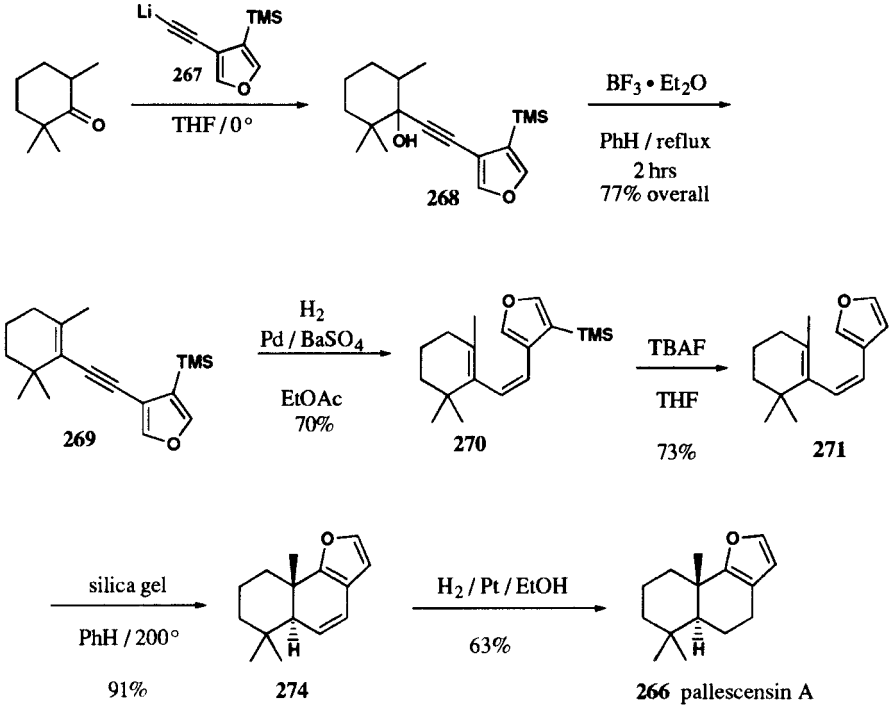
PALLESCENSIN A

Pallescensin A (**266**) has been postulated to act as part of the defense mechanism of opisthobranch molluscs. These molluscs concentrate sponge metabolites in skin glands and release them in



266 pallescensin A

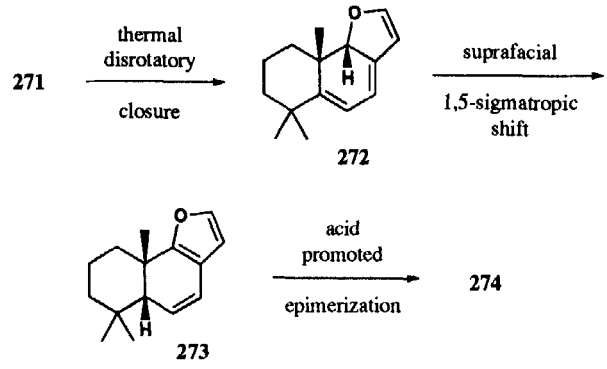
defensive secretions when endangered.[83] Because of its classical ring structure pallescensin A has attracted a large amount of attention. Since the first synthesis by Matsumoto in 1978,[84] a variety of approaches have proved successful. The strategy followed by Liotta[85] involves as a key step an electrocyclic ring closure of a furyl diene to obtain the pallescensin A skeleton (Scheme 49). Addition of



Scheme 49. *Liotta Synthesis of Pallescensin A*

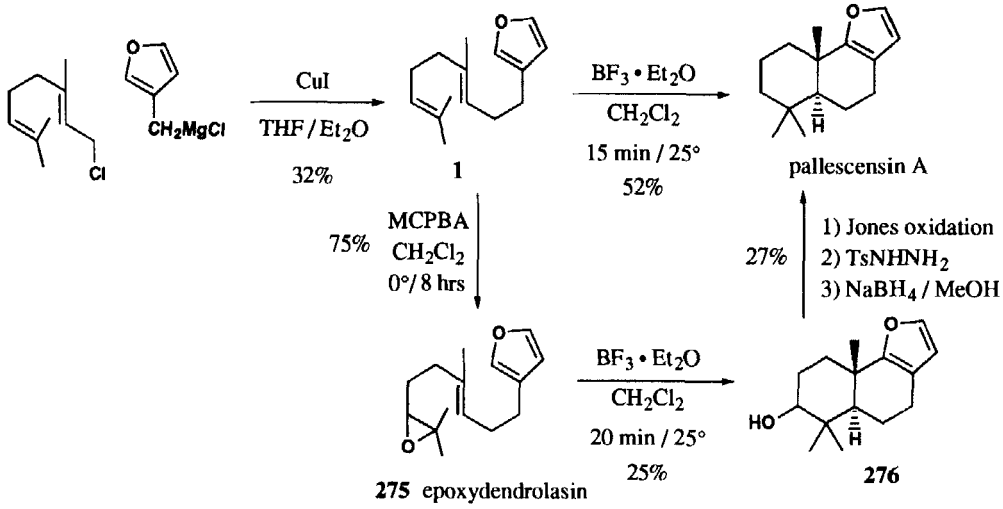
furylacetylide **267** to 2,2,6-trimethylcyclohexanone gave propargylic alcohol **268**. BF_3•Et_2O promoted elimination of water produced enyne **269** in 77% overall yield. Reduction of the alkyne with Lindlar catalyst afforded *(Z)*-diene **270**. Overreduction of the furan ring was minimized by the presence of the TMS group. Desilylation of **270** with TBAF produced the key intermediate **271**. Thermally-allowed disrotatory electrocyclization followed by a suprafacial [1,5]-hydrogen shift produced the *cis*-decalin

(273, below) which could be isomerized in the presence of various acids to give the more stable



trans-decalin system **274**. Selective catalytic hydrogenation of **274** using less than one equivalent of hydrogen, afforded pallescensin A in quantitative yield based on recovered alkene. An overall yield of approximately 23% was obtained in the 6 step procedure.

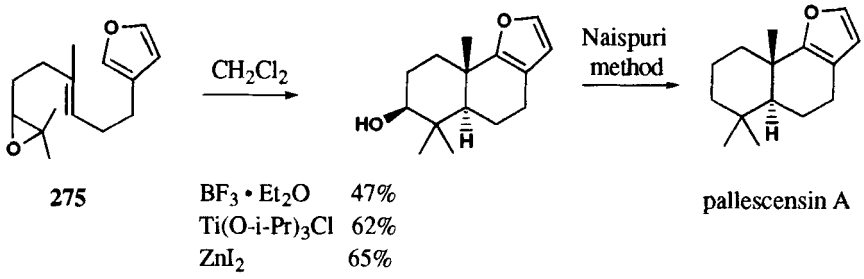
A biomimetic approach to pallescensin A beginning from dendrolasin has been developed by Naispuri[86] (Scheme 50). Coupling of 3-furymethylmagnesium chloride with geranyl chloride in the



Scheme 50. *Naispuri Approach to Pallescensin A via Dendrolasin*

presence of cuprous iodide affords dendrolasin (**1**) in 32% yield. Treatment of **1** with BF_3•Et_2O provided pallescensin A and an olefinic impurity in an 84:16 ratio. Removal of the impurity by chromatography on silver-impregnated silica gave pallescensin A in 17% overall yield for the 2 steps. The synthesis can be completed in a more stereospecific manner by cyclization of epoxydendrolasin **275** Treatment of **275** with BF_3•Et_2O yielded alcohol **276**. Deoxygenation of the alcohol is achieved by Jones oxidation, tosylhydrazone formation and sodium borohydride reduction to provide pallescensin A in 6 steps and 1.6% yield. An improvement on the cyclization step has been made by Tanis.[87]

Higher yields in the cyclization of epoxydendrolasin can be obtained through the use of zinc iodide or $Ti(Oi\text{-}Pr)_3Cl$ (Scheme 51).



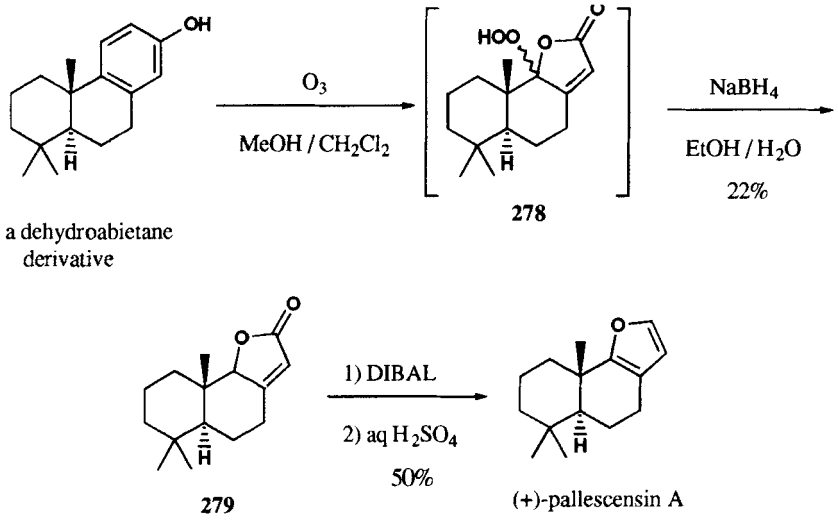
275

$BF_3 \cdot Et_2O$ 47%
$Ti(O\text{-}i\text{-}Pr)_3Cl$ 62%
ZnI_2 65%

pallescensin A

Scheme 51. *Tanis Modification*

A short enantiospecific synthesis of (+)-pallescensin A has been developed by Oishi using the chiral pool approach (Scheme 52).[88] Ozonolysis of the readily available dehydroabietane derivative



277 a dehydroabietane derivative

278

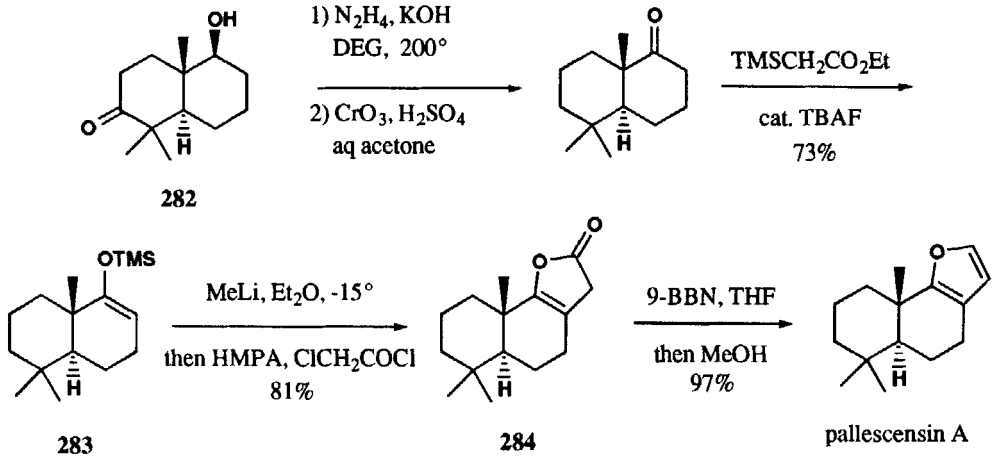
279

(+)-pallescensin A

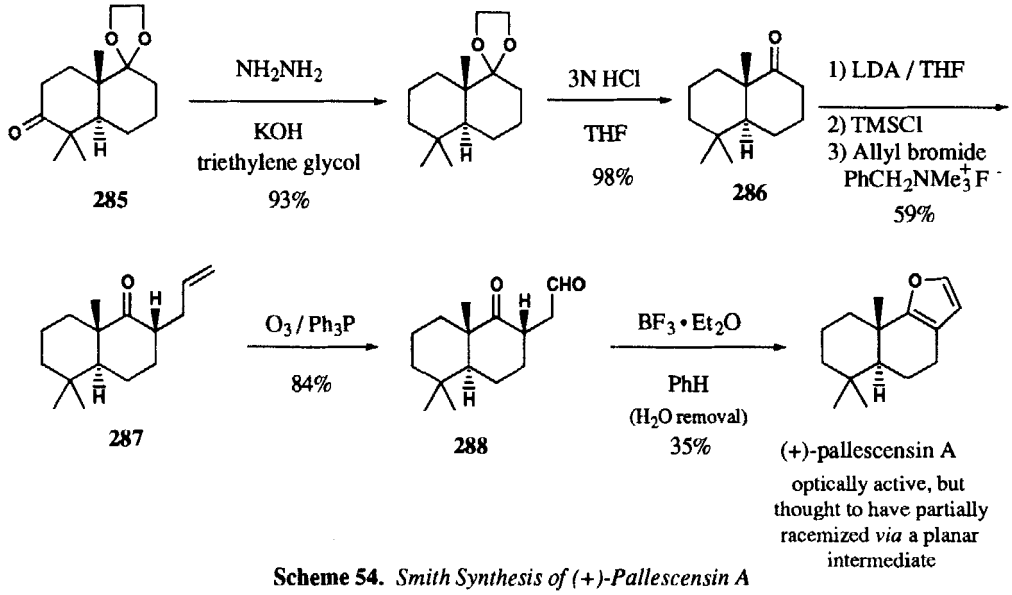
Scheme 52. *Oishi Synthesis of (+)-Pallescensin A*

277 provided the hydroperoxybutenolide **278**. Sodium borohydride reduction gave butenolide **279** which upon further reduction with DIBAL and treatment with aqueous sulfuric acid stereospecifically provided (+)-pallescensin A. An overall yield of 11% was obtained over 3 steps.

Gariboldi and coworkers[89] produced pallescensin A starting from the known hydroxy ketone **282** (Scheme 53).[90] Proceeding in a straightforward manner, **282** was converted to the silyl enol ether **283**. Furan ring annulation using their previously developed methodology gave the unsaturated lactone **284** which was readily reduced and dehydrated to pallescensin A. Two years later, Smith reported a slight variation of this approach which provided optically enriched material (Scheme 54).[91] The optically pure trans-decalone **285** was converted to pallescensin A, also by appending the furan



Scheme 53. *Gariboldi Synthesis of Pallescensin A*

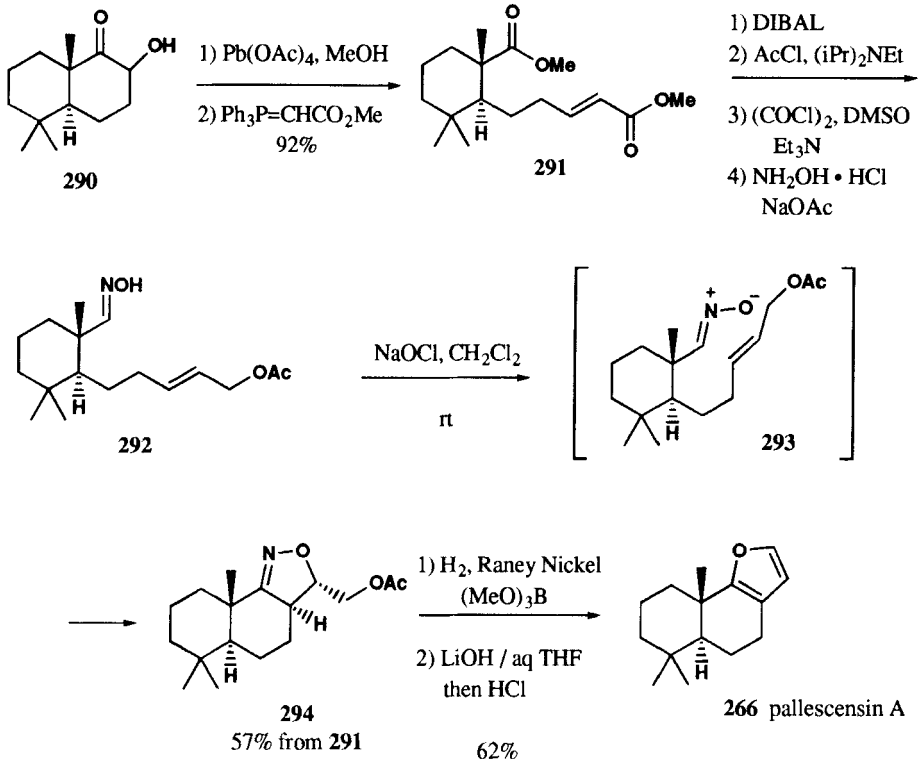


Scheme 54. *Smith Synthesis of (+)-Pallescensin A*

ring *via* an annulation process. Wolff-Kishner reduction of ketone **285**, available from the Wieland-Miescher ketone, and hydrolysis proceeded to ketone **286**. Attempted alkylation of **286** using standard methodology results in the formation of a mixture of monoalkylated and dialkylated products along with recovered starting material. Monoalkylation was achieved *via* the TMS enol ether by treatment with a fluoride source and allyl bromide resulting in a 1:1 mixture of diastereomers which could be equilibrated with base to a 98:1 mixture in favor of the desired diastereomer. Ozonolysis of **287** to

give the aldehyde **288** and treatment with $BF_3 \cdot Et_2O$ afforded partially racemized pallescensin A in 9 steps from the Wieland-Miescher ketone and 16% overall yield from ketal **285**.

Most recently, Shishido has produced **266** using intramolecular 1,3-dipolar cycloaddition (Scheme 55).[92] Manipulation of the optically active Wieland-Miescher ketone gave the previously



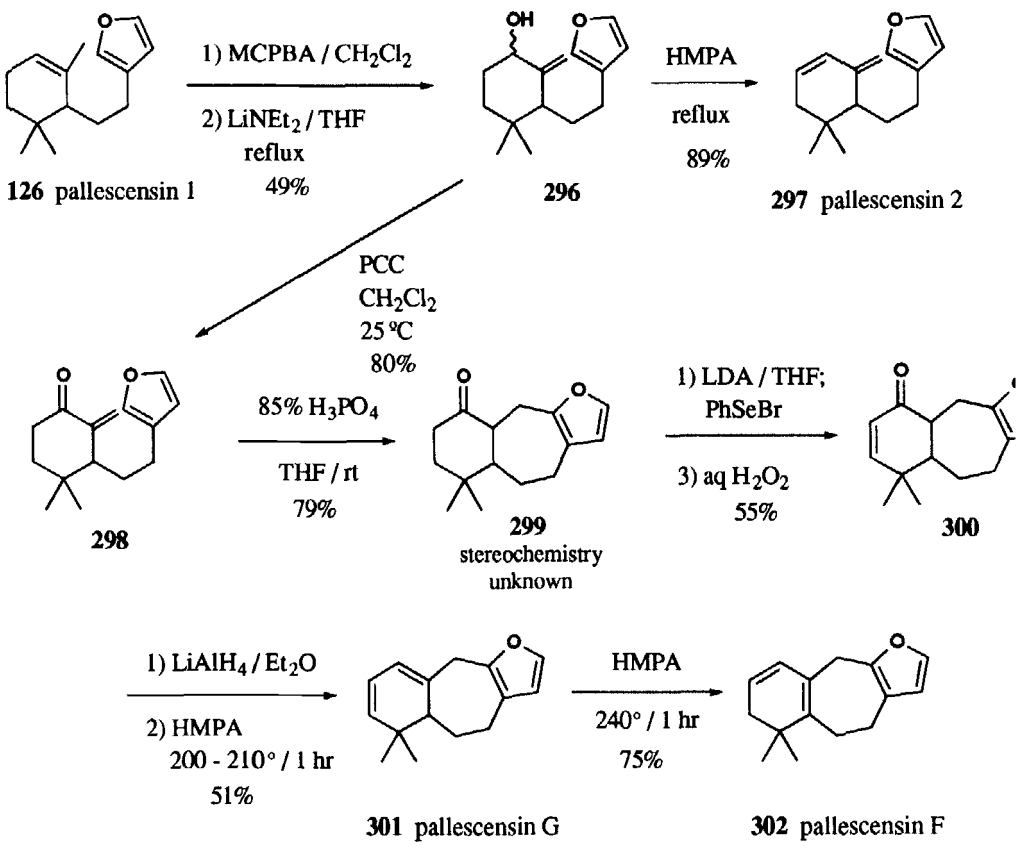
290 **291** **292** **293** **294**

Scheme 55. *Shishido Synthesis of Pallescensin A*

known hydroxyketone **290**. Oxidative cleavage and trapping of the unstable aldehyde in an olefination process gave the *trans* ester **291**. Dibal was used to reduce both esters down to the alcohol stage where selective acetylation gave only the acetate of the allylic alcohol. Swern oxidation of the remaining alcohol and treatment with hydroxylamine hydrochloride gave the oxime **292**. Treatment of **292** with sodium hypochlorite produced the hydroxamoyl chloride which underwent loss of HCl to produce the nitrile-oxide **293**. Intramolecular cycloaddition gave the isoxazoline **294** in an excellent 57% yield from **291**. Hydrogenolysis of the N-O bond and ring closure *via* a standard series of processes gave optically enriched (+)-pallescensin A.

PALLESCENSINS -2, F AND G

Matsumoto extended an enantiospecific synthesis of pallescensin-1 to provide pallescensins -2, F and G, as shown in Scheme 56.[93] Epoxidation of pallescenisn-1 and eliminative epoxide opening by treatment with lithium diethylamide produced alcohol **296** as a mixture of diastereomers. Addition

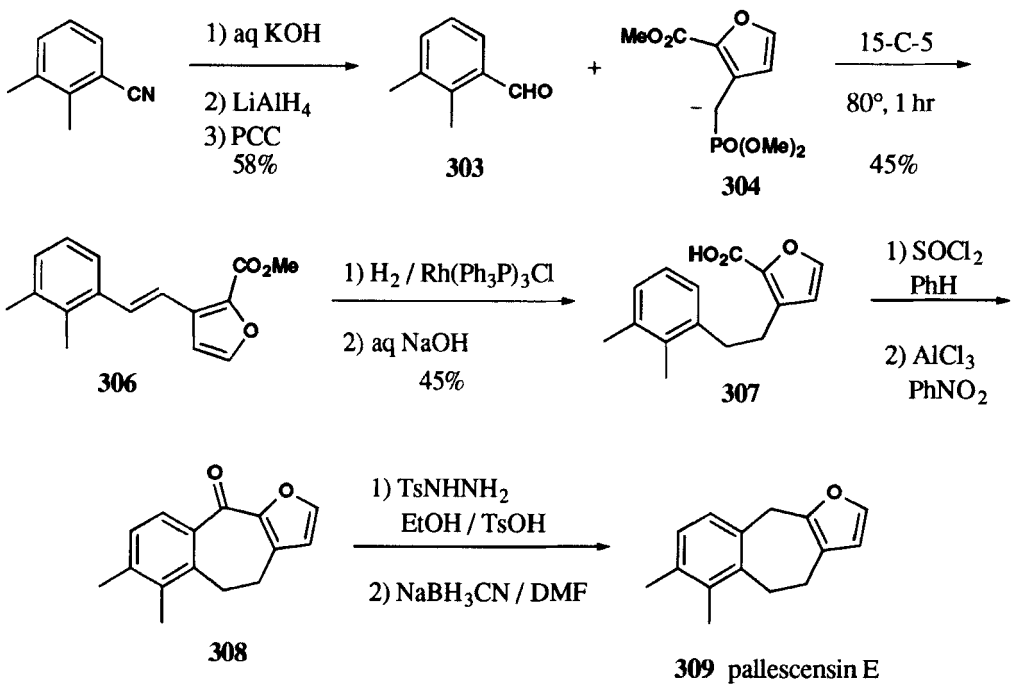


Scheme 56. *Matsumoto Syntheses of Pallescensins 2, F and G*

of **296** to refluxing HMPA resulted in elimination to give pallescensin-2 (**297**) in 44% overall yield from pallescensin-1 and in a total of 6 steps and 2.4% overall yield from optically pure cyclocitral. Pallescensins G and F were also prepared from alcohol **296** by oxidation with PCC to the branchpoint enone **298**. Phosphoric acid-promoted cyclization resulted in the tricyclic ketone **299** in 79% yield, excellent for a furan-terminated cation-olefin cyclization giving a seven-membered ring. Unsaturated ketone **300** was obtained in 50% yield by selenoxide elimination. Reduction of **300** to the alcohol and elimination afforded pallescensin G (**301**) in 11 steps and 0.5% overall yield from cyclocitral. Further heating of **301** in HMPA equilibrated the diene system to give pallescensin F (**302**) in a total of 12 steps and 0.36% overall yield.

PALLESCENSIN E

The related metabolite pallescensin E has been synthesized by Baker and Sims[94] and is illustrated in Scheme 57. A cation-olefin cyclization was also used to effect the key bond formation. Basic hydrolysis of 2,3-dimethylbenzonitrile and a subsequent reduction-oxidation sequence provided aldehyde **303**. The Wadsworth-Emmons olefination of phosphonate **304** with aldehyde **303** was found to

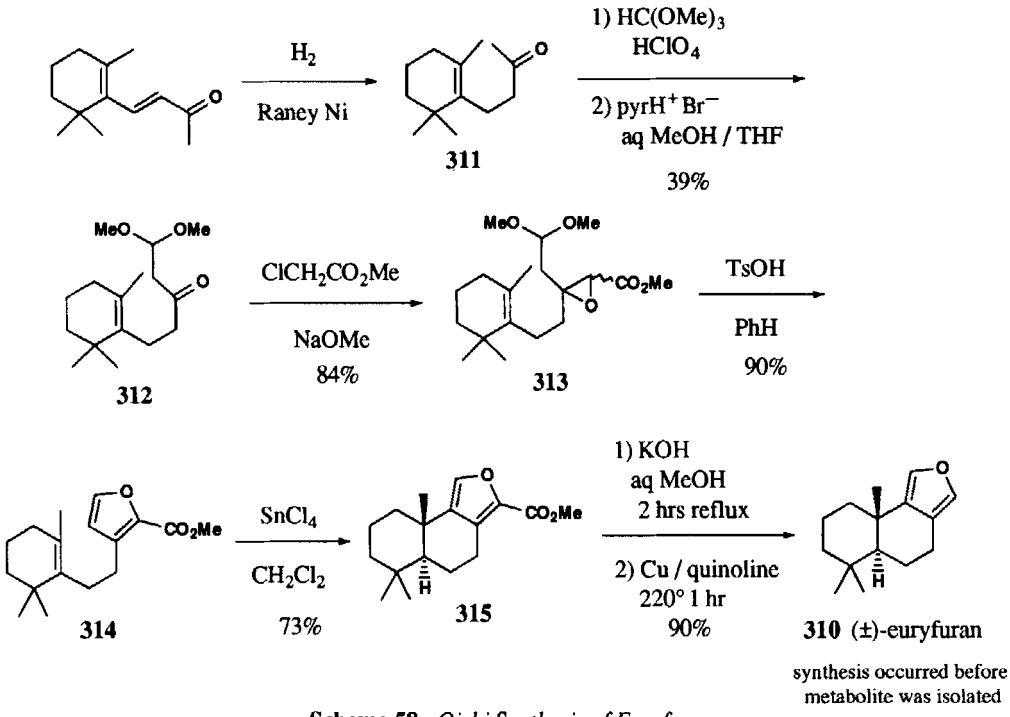


Scheme 57. *Baker Synthesis of Pallescensin E*

only occur in the presence of catalytic amounts of 15-crown-5. Hydrogenation of the resulting stilbene **306** was followed by saponification of the ester to provide acid **307**. Formation of the acid chloride and reaction with aluminum chloride in nitrobenzene gave ketone **308** *via* an intramolecular Friedel-Crafts acylation. Removal of the carbonyl by formation of the tosylhydrazone and reduction with sodium cyanoborohydride yielded pallescensin E (**309**) in a 10 step process.

EURYFURAN

Euryfuran (**310**) has been isolated as the (-)-form from the nudibranchs *Hypselodoris californiensis* and *H. porterae*[95] and as the (+)-form from the sponges *Dysidea herbacea* and *Euryspongia* species.[96] Interest in euryfuran stems primarily from its structural similarity to the drimane sesquiterpenoids, such as warburganal and polygodial. The syntheses of **310** by Oishi and by Nakano appeared before the natural product had been isolated. In Oishi's 1979 synthesis of confertifolin[97] euryfuran was prepared as an intermediate (Scheme 58). The synthesis began with the partial hydrogenation of β-ionone to afford the nonconjugated enone **311**. Reaction of **311** with trimethyl orthoformate and 70% perchloric acid gave a mixture of products which was converted to acetal **312** upon treatment with pyridinium hydrobromide in aqueous methanol. Darzens condensation with methyl chloroacetate

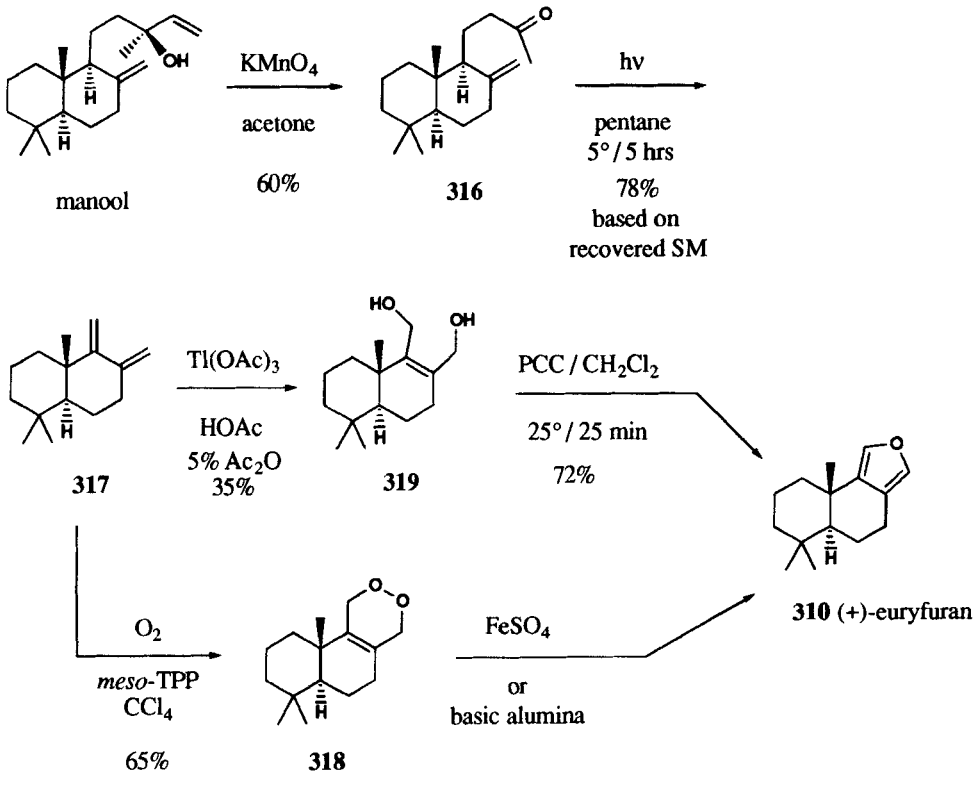


Scheme 58. *Oishi Synthesis of Euryfuran*

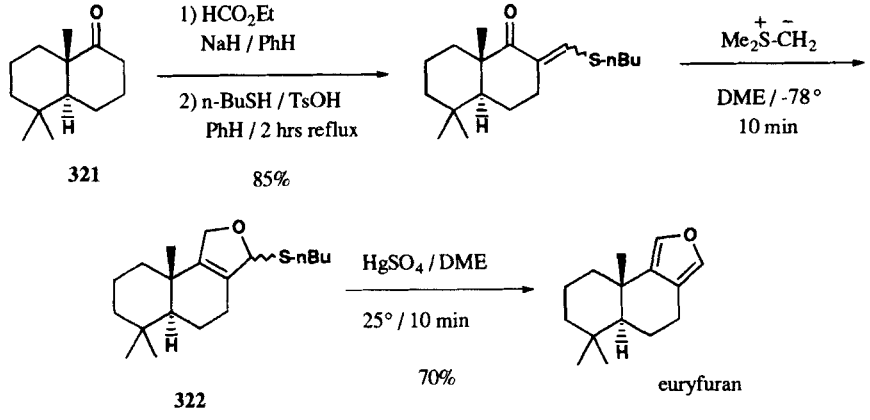
yielded the epoxide isomers **313**. Rearrangement with catalytic TsOH produced the furan **314**. Treatment with Lewis acid promoted ring closure to ester **315**. Saponification of the ester followed by decarboxylation gave euryfuran in 8 steps and 19% overall yield.

Also in the process of developing a synthesis of confertifolin, Nakano[98] prepared peroxide **318**, which was converted to euryfuran (Scheme 59). Permanganate oxidation of manool yielded the ketone **316** in 60% yield. Upon irradiation in pentane **316** underwent a Norrish type II cleavage to give diene **317** in 78% yield based on recovered ketone. Singlet oxygen oxidation in the presence of *meso*-tetraphenylporphine provided cyclic peroxide **318**. Upon treatment with basic alumina or ferrous sulfate **318** was converted to (+)-euryfuran, thus providing a 3-step enantiospecific synthesis of this metabolite. Alternatively,[99] oxidation of intermediate diene **317** with thallium(III) acetate afforded diol **319** in 35% yield. Oxidation-dehydration by treatment with PCC produced (+)-euryfuran in 4 steps and 12% overall yield.

Ley's synthesis[100] of euryfuran is outlined in Scheme 59a. In a classical transformation, decalone **321** was formylated and converted to the *n*-butylthiomethylene derivative and reaction with trimethylsulfonium methylide at -78° provided dihydrofuran **322** *via* the method of Spencer. Treatment of with mercuric sulfate provided racemic euryfuran in 60% overall yield from **321**.



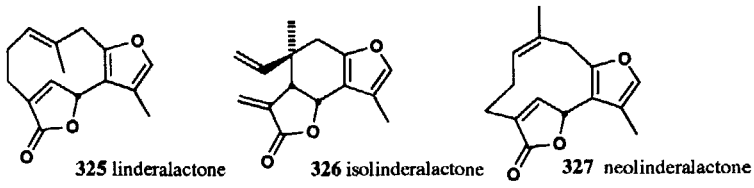
Scheme 59. *Nakano Syntheses of (+)-Euryfuran*



Scheme 59a. *Ley Synthesis of Racemic Euryfuran*

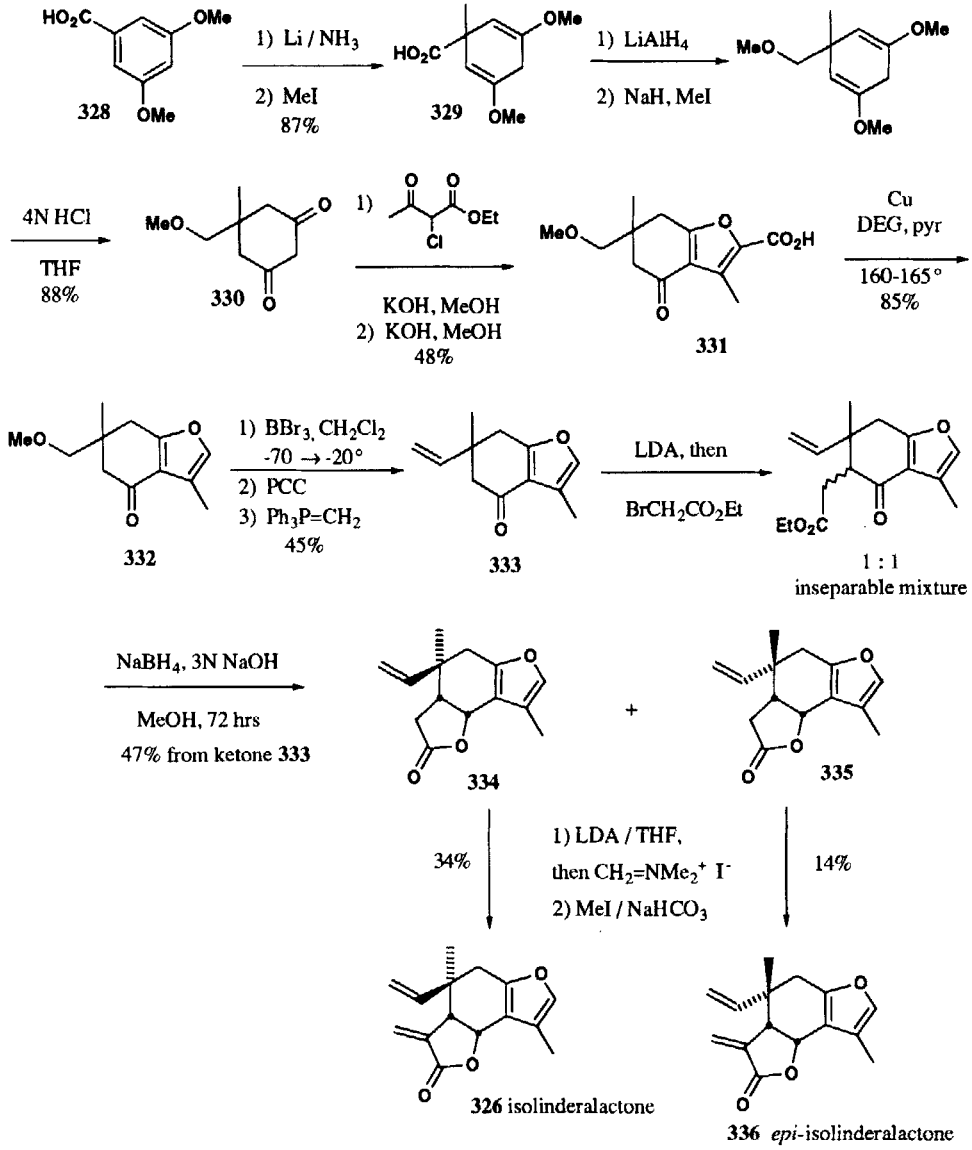
LINDERALACTONES

Takeda isolated the germacrane furanosesquiterpenes linderalactone (**325**), isolinderalactone (**326**) and neolinderalactone (**327**)[101] from the shrub *Lindera strychnifolia* and demonstrated the Cope

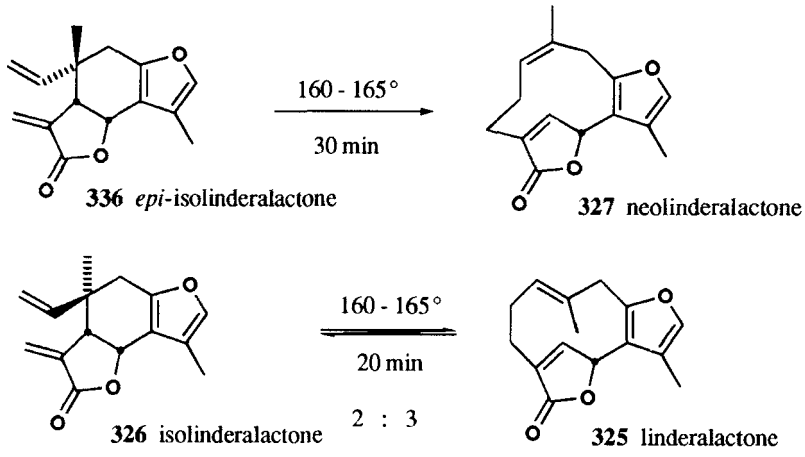


325 linderalactone **326** isolinderalactone **327** neolinderalactone

rearrangement relationships between these metabolites.[102] Given this starting point, Magnus has synthesized **325-327** using Cope rearrangement as the vehicle for producing the 10-membered rings in **325** and **327** *via* ring expansion (Schemes 60 and 61).[103] Targeting isolinderalactone and *epi*-isolin



Scheme 60. *Magnus Linderalactone Synthesis*

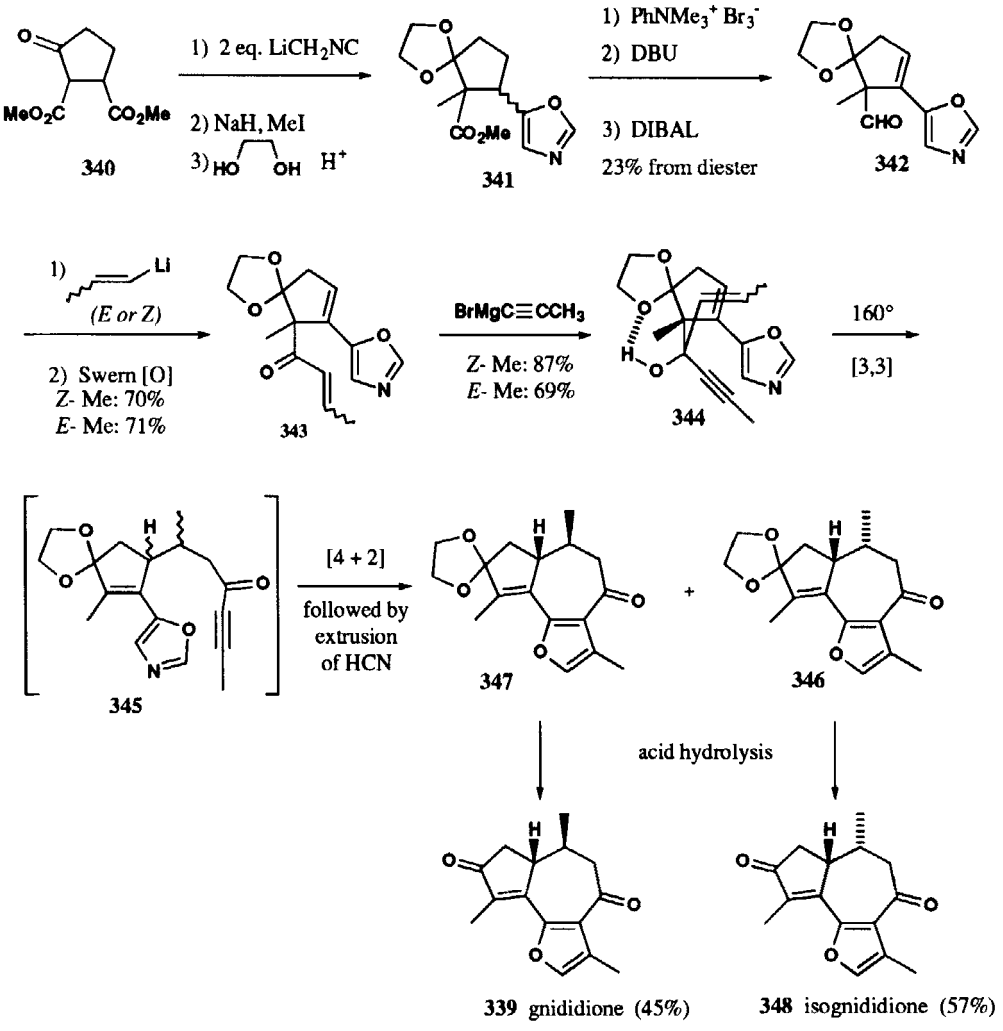


Scheme 61. *Cope Rearrangements of Linderalactones*

deralactone as precursors to the germacranolide skeleton, the benzoic acid **328** was Birch reduced and alkylated *in situ* with CH_3I to provide the cyclohexadiene **329** which was routinely taken on to the cyclohexanedione **330**. Furan ring annulation was accomplished using the method of Stetter[104] providing **331** which was decarboxylated to **332**. The lactone was annulated classically leading to the diastereomers **334** and **335** which were methylenated to the naturally occurring isolinderalactone and *epi*-isolinderalactone **336**, respectively. Heating of the latter (Scheme 61) resulted in complete conversion to neolinderalactone *via* Cope rearrangement, while a 2:3 equilibrium mixture of **325** and **326** could be generated by heating isolinderalactone. This very pretty sequence is marred by the somewhat routine transformations of lactones to α-methylene lactones which proceeded in low yields.

GNIDIDIONE

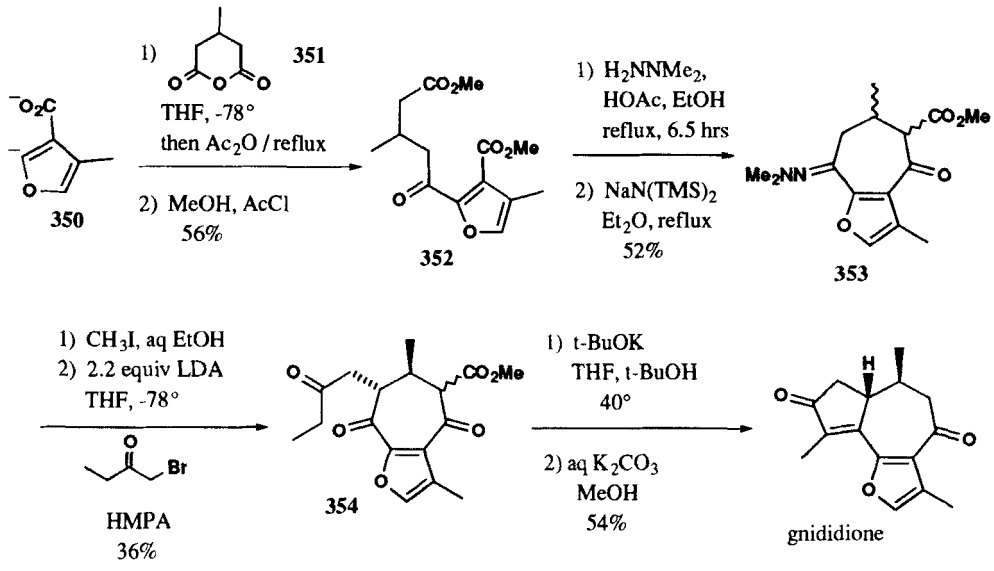
The guaiane furanosesquiterpene gnididione (**339**) was isolated from the antileukemic fractions of *Gnidia latifolia* by Kupchan[105] and was the first example of a furan-containing metabolite in its skeletal class. The synthesis was accomplished neatly by Jacobi[106] utilizing a cascade of three pericyclic processes (Scheme 62). The known diester **340**[107] was regiospecifically converted to the isoxazole **341** using lithiomethylisocyanide. Unsaturation was introduced by a bromination-dehydrobromination sequence and the remaining ester was converted to the aldehyde **342**. At this point, the aldehyde was added to both *Z* and *E*-lithiopropene followed by an oxidation to the enone in each case giving the *E* and *Z* enones **343** in comparable yields. A key reaction of each enone with propynylmagnesium bromide gave the intermediate alcohols **344** as the major diastereomers with only minor amounts (<4%) of the other isomers. Chelation control involving the *syn*-ketal oxygen atom in the addition was invoked to explain the stereoselectivity. Heating the *E* and *Z* isomers to 160° first induced a Cope rearrangement *via* a chelated chair transition state leading to the intermediate respective ynones **345** (*E* -**344** → **346** and *Z* -**344** → **347**). These intermediate compounds could be isolated when the thermolysis was carried out at 110°. At the higher temperature however, the isomeric **345's**



Scheme 62. *Jacobi Synthesis of Gnididione*

independently underwent intramolecular [4+2] ynone-isoxazole cycloaddition followed by retro [4+2] extrusion of HCN leading directly to the furans **346** and **347**. These were deblocked with unspecified "mild acid hydrolysis" conditions to give racemic gnididione and isognididione.

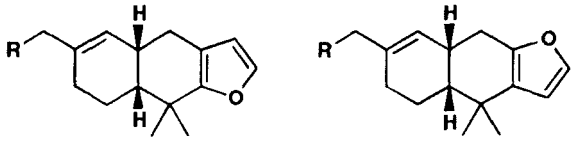
A completely different approach was used by Knight[108] in a 1990 synthesis of gnididione (Scheme 63). Electing to employ a preformed furan, the trisubstitution pattern of the furan was set in the first step in the reaction between the furoic acid dianion **350** and the anhydride **351** leading to diester **352**. Conversion to the N,N-dimethylhydrazone and Dieckmann cyclization gave the cyclo-heptanone **353** as a mixture of isomers. Removal of the dimethylhydrazone group gave a diketone (not pictured) which was alkylated as its dianion with 1-bromo-2-pentanone to give the trione **354** in 36% yield. Aldol cyclization and decarbomethoxylation gave racemic gnididione.



Scheme 63. *Knight Synthesis of Gnididione*

FURODYSIN AND FURODYSININ

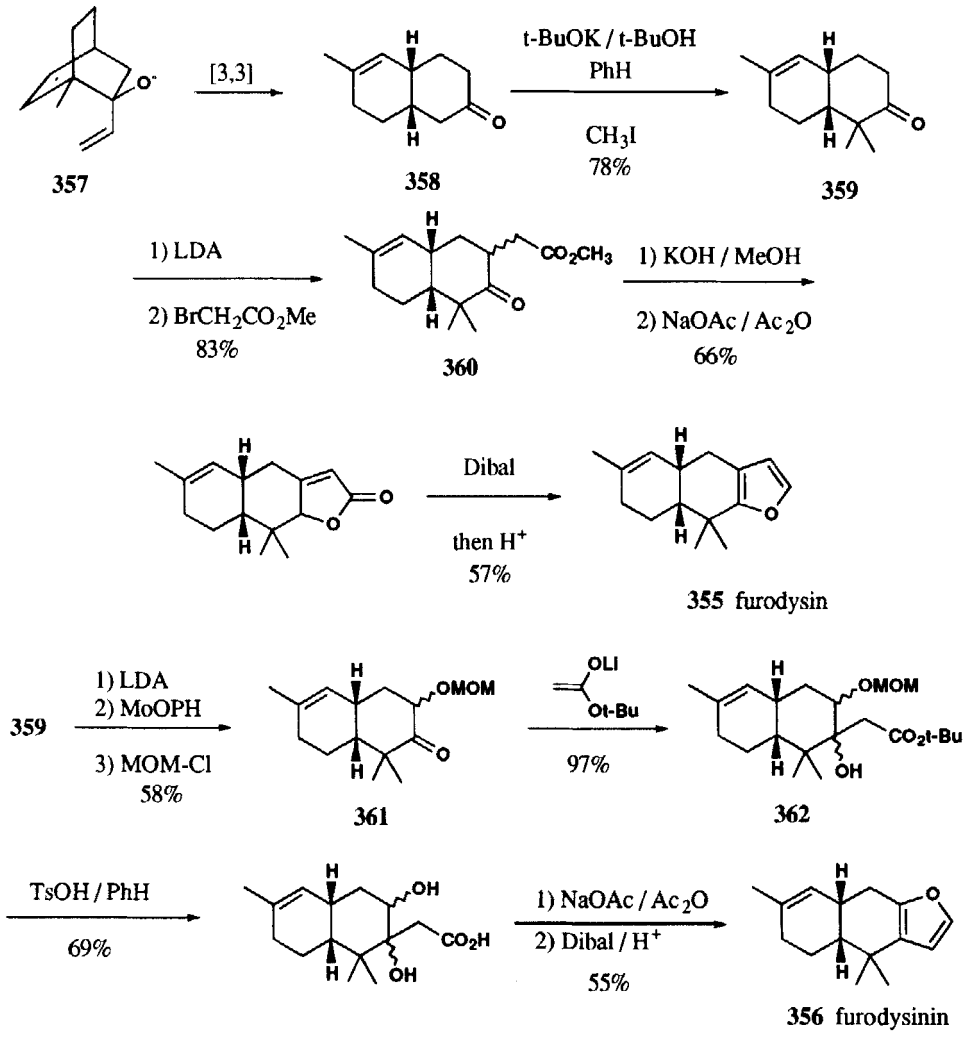
Furodysin (**355**) and furodysinin (**356**) and their thioacetyl analogs (R = AcS-) have been isolated from various species of *Dysidea* from several geographic regions.[109] Interestingly, metabolites have been isolated in both enantiomeric series from the same sponge genus. Compounds in this



355 furodysin (R = H) **356** furodysinin (R = H)

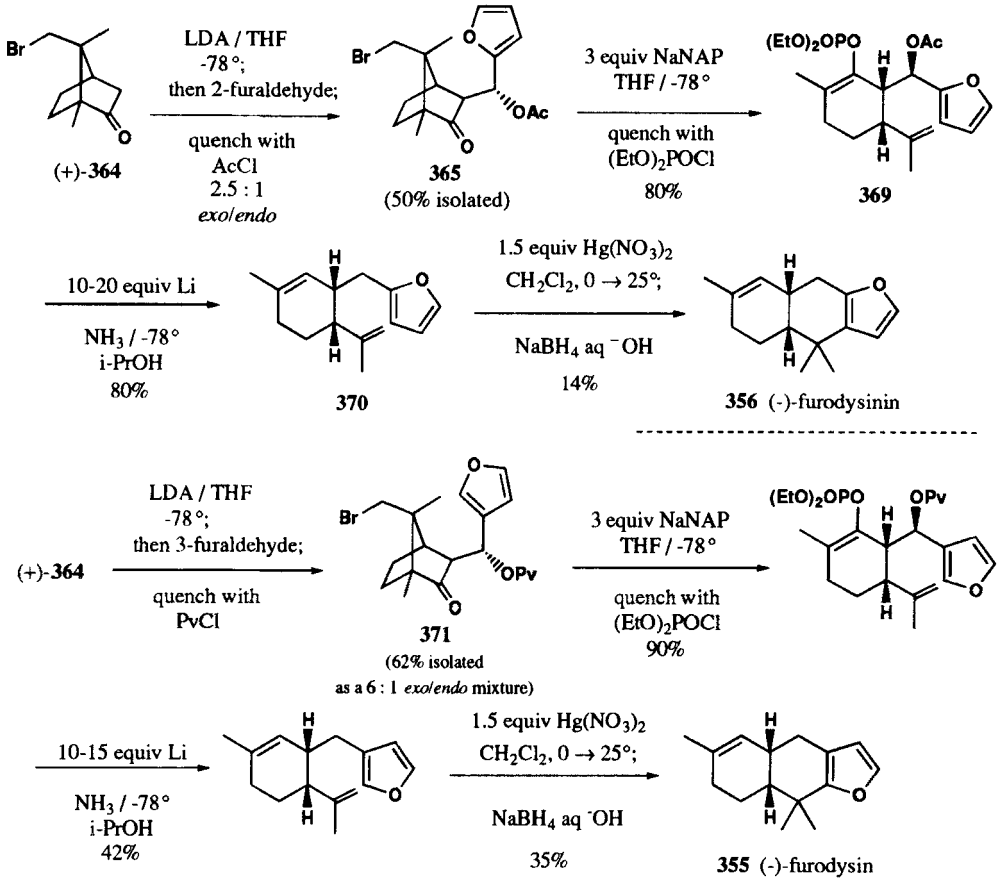
series exhibit moderate antiparasitic activity. Only the parent compounds have been synthesized so far, in both racemic and optically pure form.

The first syntheses were reported by Hirota (Scheme 64) using a common intermediate.[110] Anionic oxy-Cope rearrangement of **357** led to the *cis*-fused bicyclic ketone **358**. *gem*-Dimethylation led to the branchpoint compound **359**. Alkylation with methyl bromoacetate appended the final two carbons. Conversion of the ketoester **360** to racemic furodysin was straightforward. Synthesis of furodysinin required α-oxidation of **359** → **361**. The two carbon appendage was added as lithio *t*-butylacetate giving **362** as an inconsequential mixture of diastereomers. Conversion of **362** to racemic furodysinin was again straightforward.

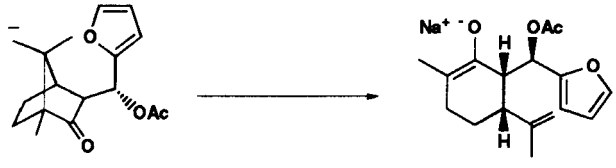


Scheme 64. *Hirota Syntheses of (±)-Furodysin and (±)-Furodysinin*

A second approach to (-)-**355** and (-)-**356** by Albizati[111] began from the readily available (+)-9-bromocamphor and led to the two metabolites *via* 4-step pathways (Scheme 65). Aldol reaction of the enolate of **364** with 2-furaldehyde and trapping of the enolate with acetyl chloride led to primarily the *exo-threo* adduct **365** which could be isolated by recrystallization. Treatment of **365** with the electron transfer agent sodium naphthalenide in THF at low temperature resulted in fragmentation of the system to the enolate **367**, presumably by way of the anion **366**. The enolate **366** could be trapped *in situ* with diethyl chlorophosphate to give the vinyl phosphate **369**. Reductive cleavage of both the phosphate and acetate groups was accomplished by Li/NH_3 to give the limonene derivative **370**. Cation-olefin cyclization initiated by mercuric nitrate followed by a reductive workup led to optically pure (-)-furodysinin in 14% yield. In an analogous fashion, aldol reaction of **364** with 3-furaldehyde



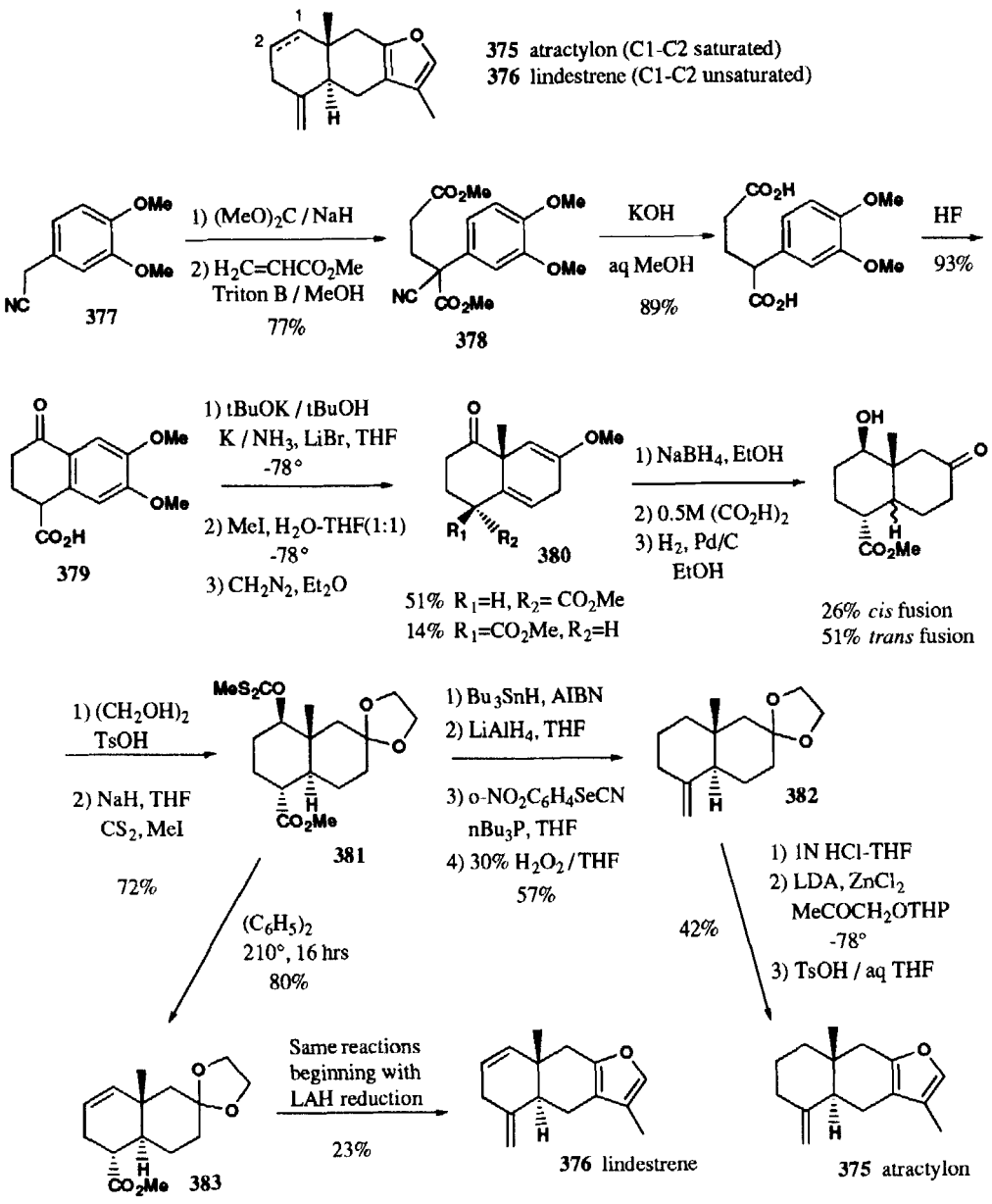
Scheme 65. *Albizati Syntheses of (-)-Furodysinin and (-)-Furodysin*



led to adduct **371**. This adduct was transformed in a near identical sequence to (-)-furodysin. These syntheses established the absolute configurations of furodysin, furodysinin and presumably the remainder of the metabolites in this family.

EUDESMANES

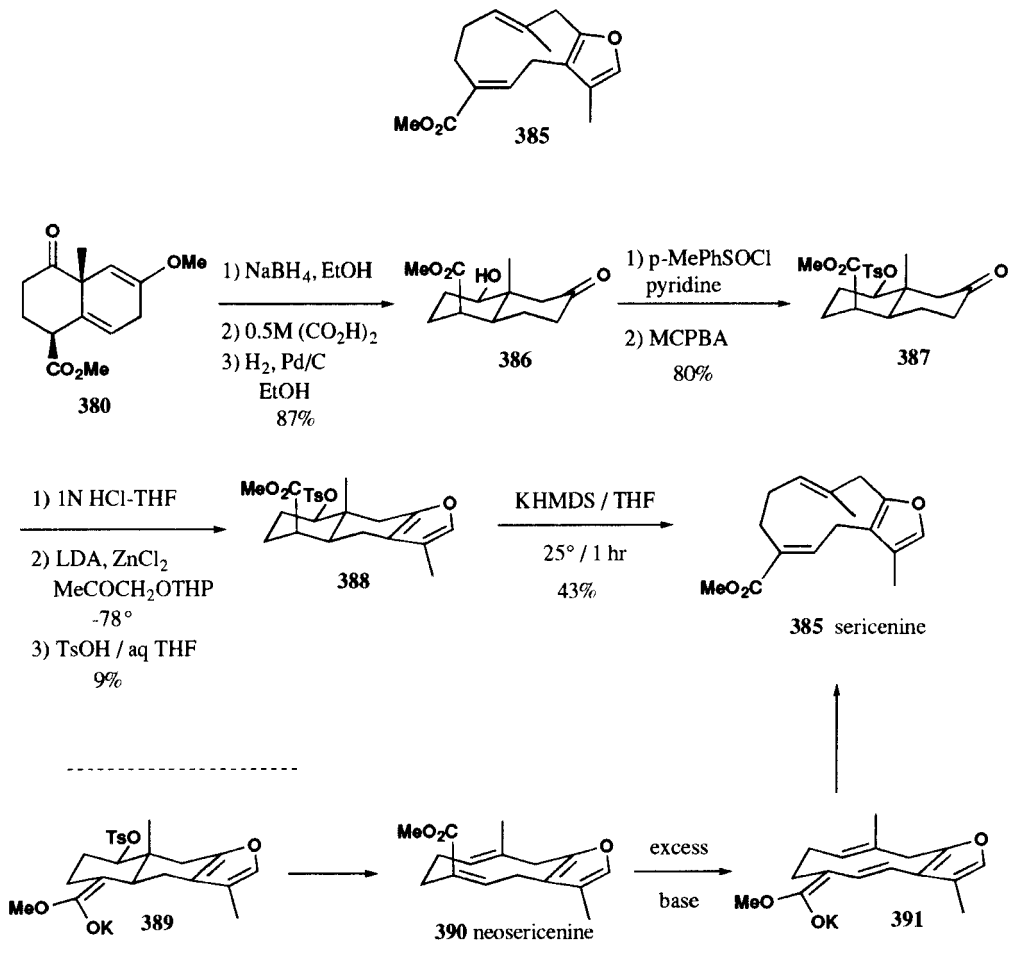
The eudesmane furanosesquiterpenes atractylon and lindestrene were isolated from various sources[112] and racemic syntheses appeared in the 1960's.[113] Utilizing the Birch reduction-alkylation approach of Mander, Honan has produced both metabolites from a common intermediate (Scheme 66).[114] Carboxymethylation of the nitrile **377** and conjugate addition to methyl acrylate produced the



Scheme 66. *Honan Syntheses of Lindestrene and Atractylon*

diester **378**. Saponification and cyclization using HF produced the tetralone **379**, substrate for a key step. Birch reduction of **379** and *in situ* alkylation with MeI produced two diastereomeric 1,4-cyclohexadienes **380** in 65% combined yield. Ketone reduction of the major isomer with $NaBH_4$ predictably gave rise to a single alcohol. However, vinyl ether hydrolysis followed by catalytic hydrogenation produced both the *trans* and *cis* fused ring systems in about a 2:1 ratio. The structure of the

major *trans* isomer was confirmed by x-ray crystallography of the derived tosylate. The key branch-point intermediate **381** was produced by standard dioxolanation of the ketone and conversion of the alcohol to the methyl xanthate. Reductive deoxygenation with nBu_3SnH removed the C1 functionality which was followed by a standard sequence for the introduction of the exocyclic olefin leading to **382** in 57% overall yield. Furan ring annulation was accomplished by alkylation of the kinetically generated enolate with tetrahydropyranyloxyacetone and acidic cyclization providing racemic atractylon. Lindestrene was produced from **381** *via* xanthate pyrolysis to provide the endocyclic olefin **383**. This intermediate was analogously carried forward to the target **376** in 23% overall yield. Honan has also taken the minor isomer of **380** from the Birch reduction-alkylation sequence and converted it to racemic sericenine **385** using a fragmentation strategy (Scheme 67). [115] Compound **380** was converted to the ketone **386** in 3 steps in 87% overall yield. Tosylation required a rare 2-step procedure providing **387**. Furan ring annulation as before gave **388** in 9% yield. Production of a dialkylation

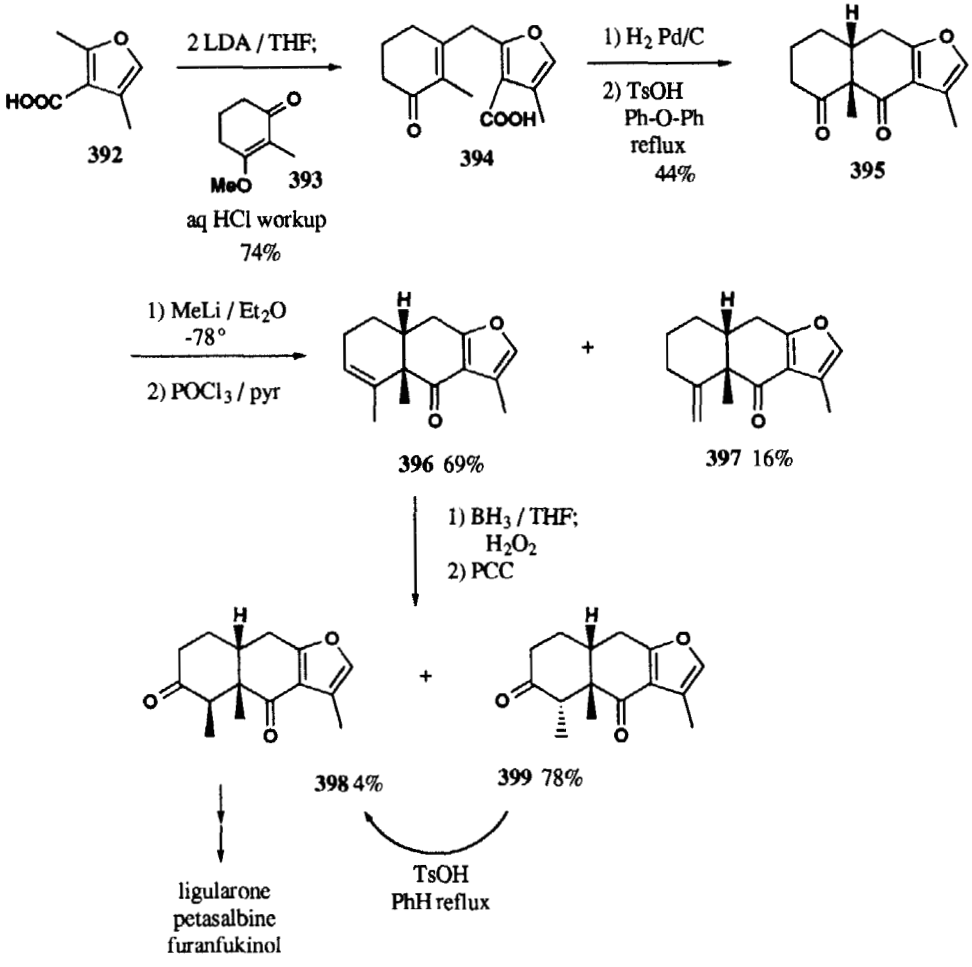


Scheme 67. *Honan Synthesis of Sericenine*

product (35%) contributed to this low yield, as did problems in an inefficient acidic cyclization step (18%), blemishing an otherwise clean and clever approach. It was stated that the initial fragmentation product might have been neosericenine **390**, a known compound,[116] but that further enolization with excess base and protonation produces the thermodynamically preferred isomer sericenine. This rationale was based on inspection of models of the intermediate dienolate **391**.

FURANOEREMOPHILANES

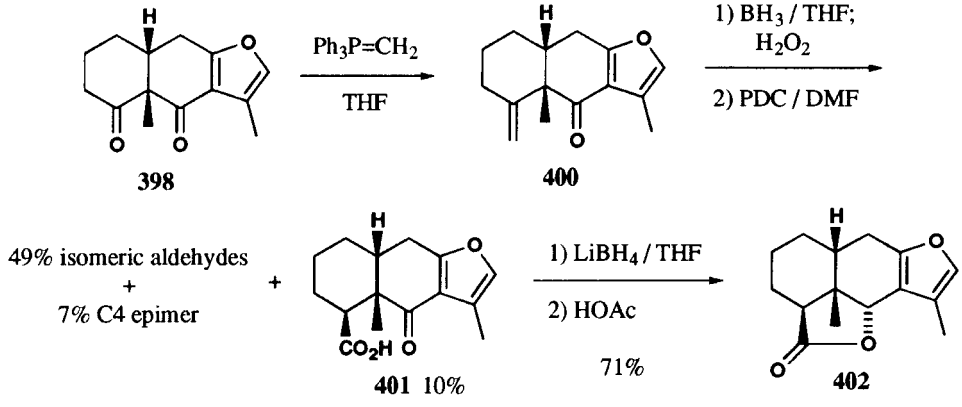
Furanoeremophilanes are common plant metabolites and several general approaches to the construction of the tricyclic ring system have been described. Tada and Takahashi have developed the dione **398** as a versatile intermediate in the production of several metabolites.[117] Using an approach which does not involve furan ring annulation, the furoic acid **392** serves as the precursor to the 2,3,4-trisubstituted furan system (Scheme 68). Double deprotonation of **392** with LDA occurs at the methyl



Scheme 68. *Tada-Takahashi Synthesis of Furanoeremophilane Derivatives*

group at the 2-position as expected and quenching with the methoxyenone **393** followed by acidic rearrangement gave the enone-acid **394**. Hydrogenation and treatment with TsOH at elevated temperature resulted in a moderate yield of the desired *cis*-fused dione **395** . Methyllithium addition was selective, occurring at the non-conjugated carbonyl, however dehydration of the resulting alcohol gave a mixture of the exocyclic and desired endocyclic isomers **397** and **396** . From **396** , hydroboration-oxidation and final oxidation with PCC gave the C4 epimeric products **398** and **399.** Fortunately, the undesired isomer **399** could be completely epimerized to the naturally occurring furanoeremophilane-3,6-dione **398**.[118] The route gave an overall yield of 17% from 2,4-dimethyl-3-furoic acid.

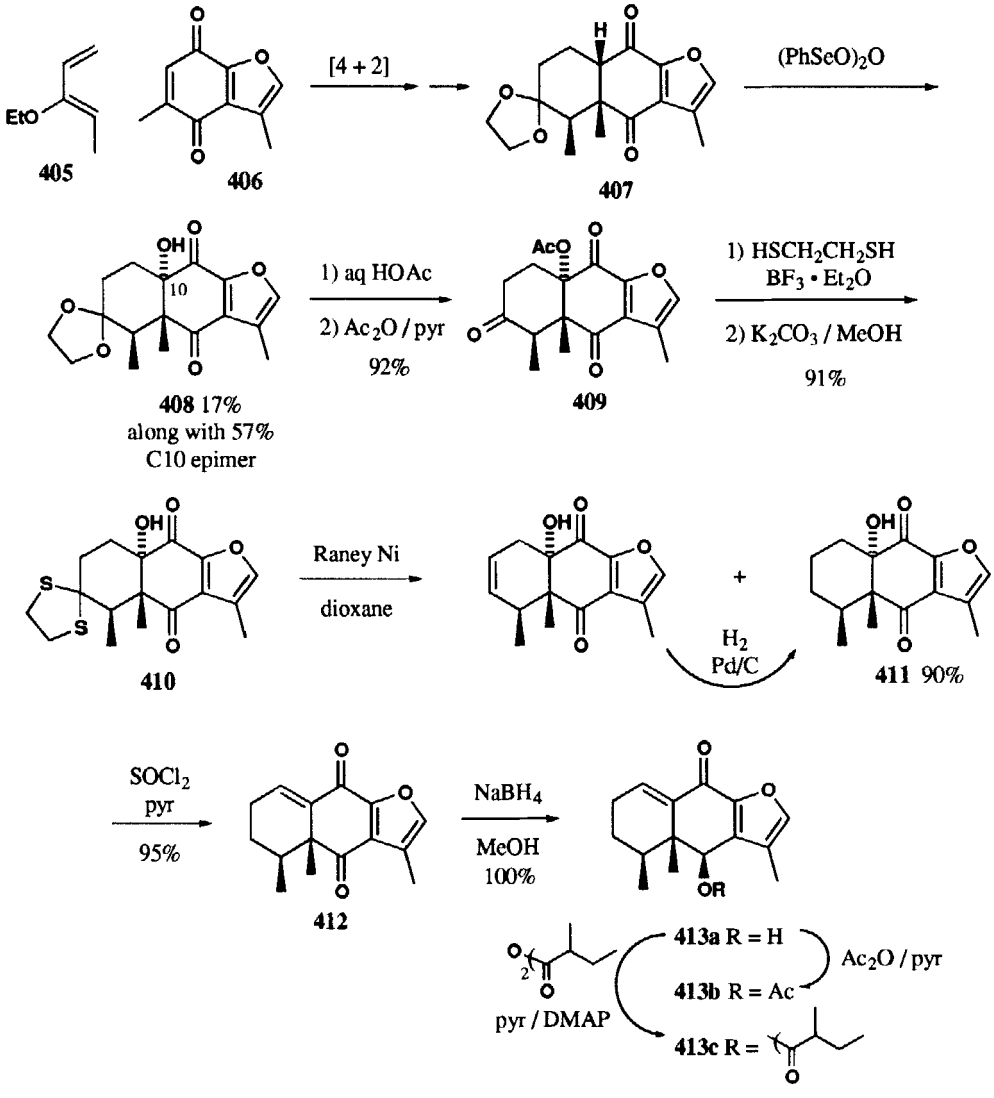
Conversion of the dione **398** into the furanoeremophilan-14β, 6α-olide (**402**)[119] appears straightforward but was hampered by an unexpected result (Scheme 69). Wittig methylenation occurs



Scheme 69. *Conversion of 398 into Furanoeremophilan-14β,6α-olide (402)*

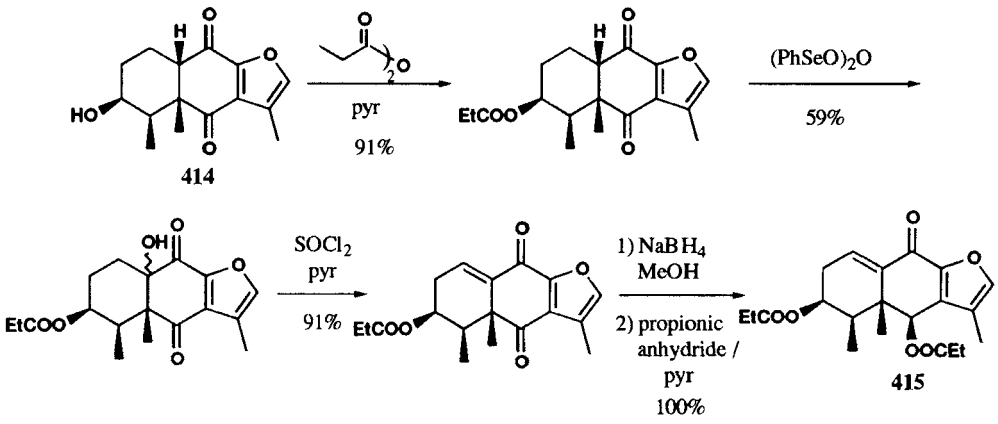
as expected. However, hydroboration-oxidation to the alcohol followed by attempted oxidation up to the acid stage with PDC gave only 10% of the desired acid **401**. Even worse, it was found that the undesired C4α derivatives could not be epimerized under either acidic or basic conditions to the desired C4β configuration. Reduction of **401** and treatment with acetic acid gave the natural product **402**, although the sequence of events here is vague because the mode of lactonization is not known with certainty.

The work of Yamakawa and Satoh in this area is substantially based on the earlier work of Bohlmann and coworkers.[120] The similar metabolites 6β-hydroxy-1,10-dehydrofuranoeremophilan-9-one (**413a**),[121] decompositin (**413b**),[122] adenostylone (**413c**)[123] and dihydrodecompositin[124] were synthesized using a Diels-Alder approach (Scheme 70). The furanoquinone **406** was cycloadded to the diene **405** to produce an adduct (not shown) which was converted in a few steps to **407**.[125] It was found that oxidation with benzeneseleninic anhydride produced a mixture of tertiary alcohols. Hydrolysis of the minor product in this mixture and acetylation gave the acetate **409**. Selective carbonyl derivatization was achieved with ethanethiol/BF_3 eventually resulting in the dithiolane **410**. Raney



Scheme 70. *Yamakawa-Satoh Furanoeremophilane Synthesis*

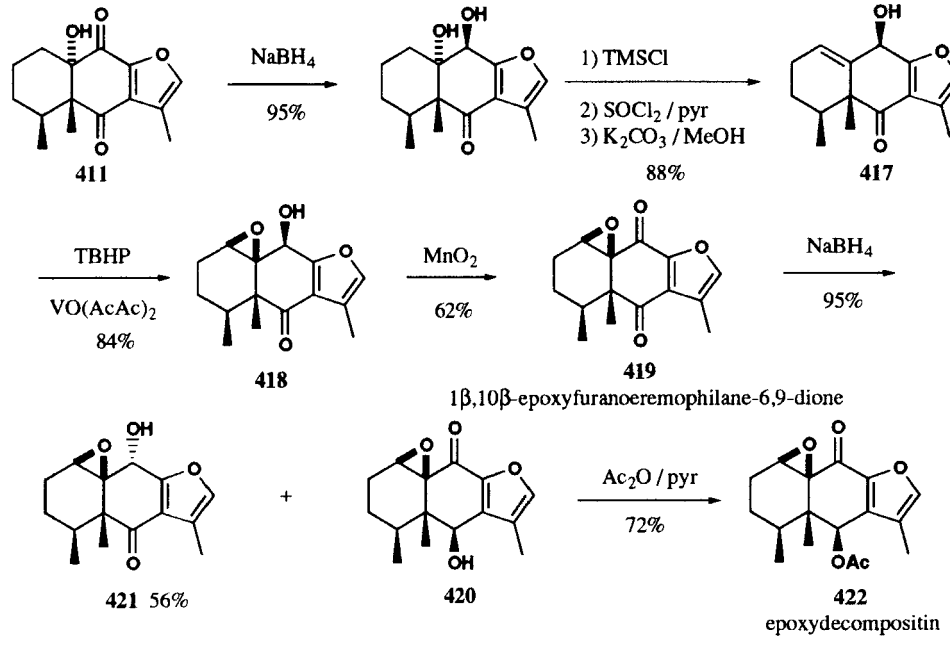
nickel desulfurization and subsequent hydrogenation achieved the desired defunctionalization to dione **411**. Dehydration gave **412** and reduction with $NaBH_4$ gave 6β-hydroxy-1,10-dehydrofuranoeremophilan-9-one (**413a**). This could be easily converted to both the propionate ester (adenostylone **413c**) and the acetate (decompositin **413b**). The compound **414** (Scheme 71), previously prepared by



Scheme 71. *Yamakawa-Satoh Synthesis of Euryops Metabolite* ***415***

Bohlmann, could be converted in a straightforward fashion to racemic 3β, 6β-dipropionyloxyeuryopsin-9-one (**415**), a metabolite of *Euryops lateriflorus*.[126]

The dione **411** served as an intermediate in the syntheses[127] of epoxyfuranoeremophilanes **419**[128] and **422** (epoxydecompositin).[129] The requisite β-epoxide (Scheme 72) was installed by hydroxyl-directed t-butylhydroperoxide/$VO(AcAc)_2$ epoxidation of **417** leading to **418** as the sole

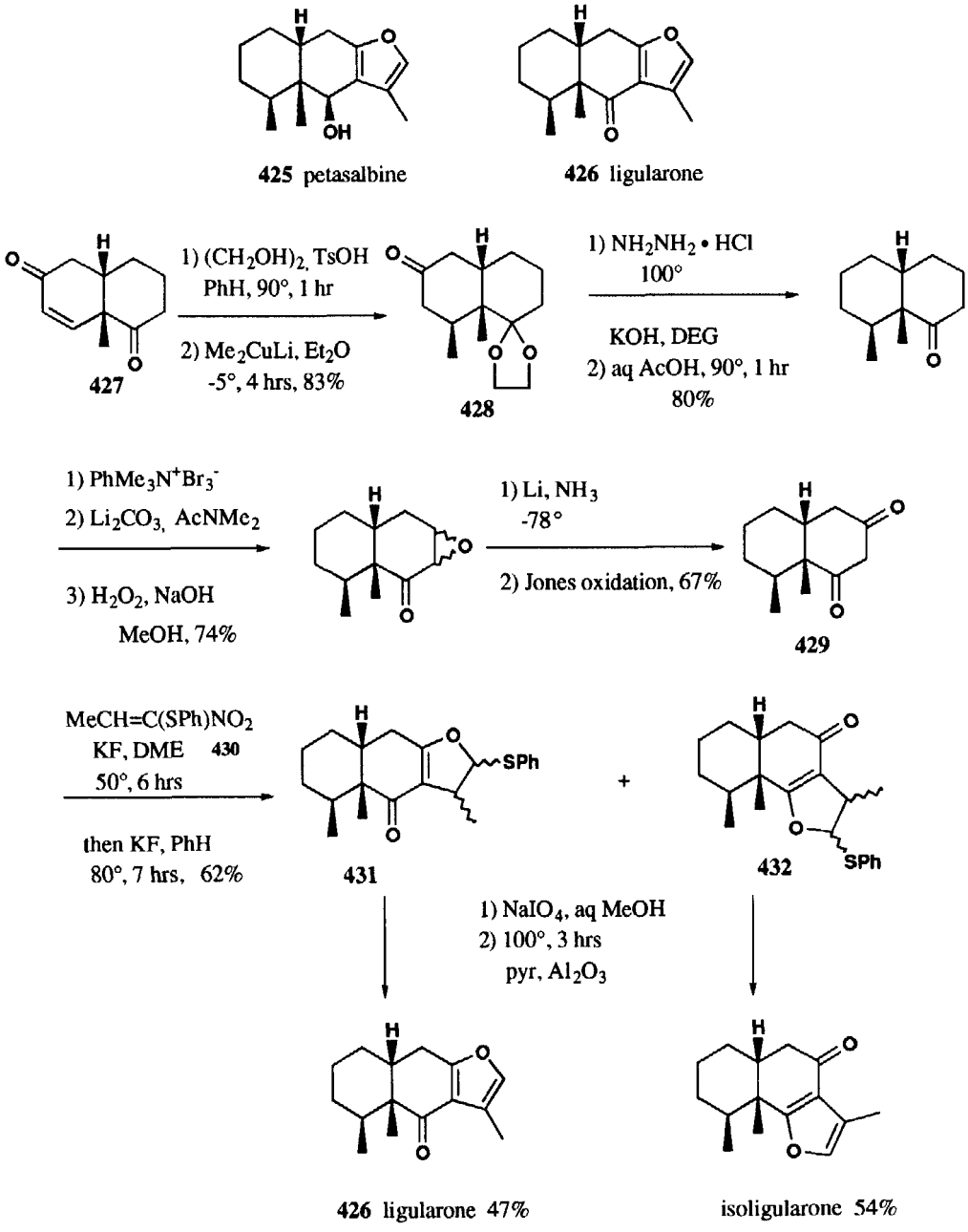


Scheme 72. *Yamakawa-Satoh Syntheses of* ***419*** *and* ***422***

isomer observed. MnO_2 oxidation gave the naturally occurring dione (**419**), however $NaBH_4$ reduction led to a regioisomeric mixture of **420** and the undesired **421**. Acetylation gave epoxydecompositin.

LIGULARONE-PETASALBINE

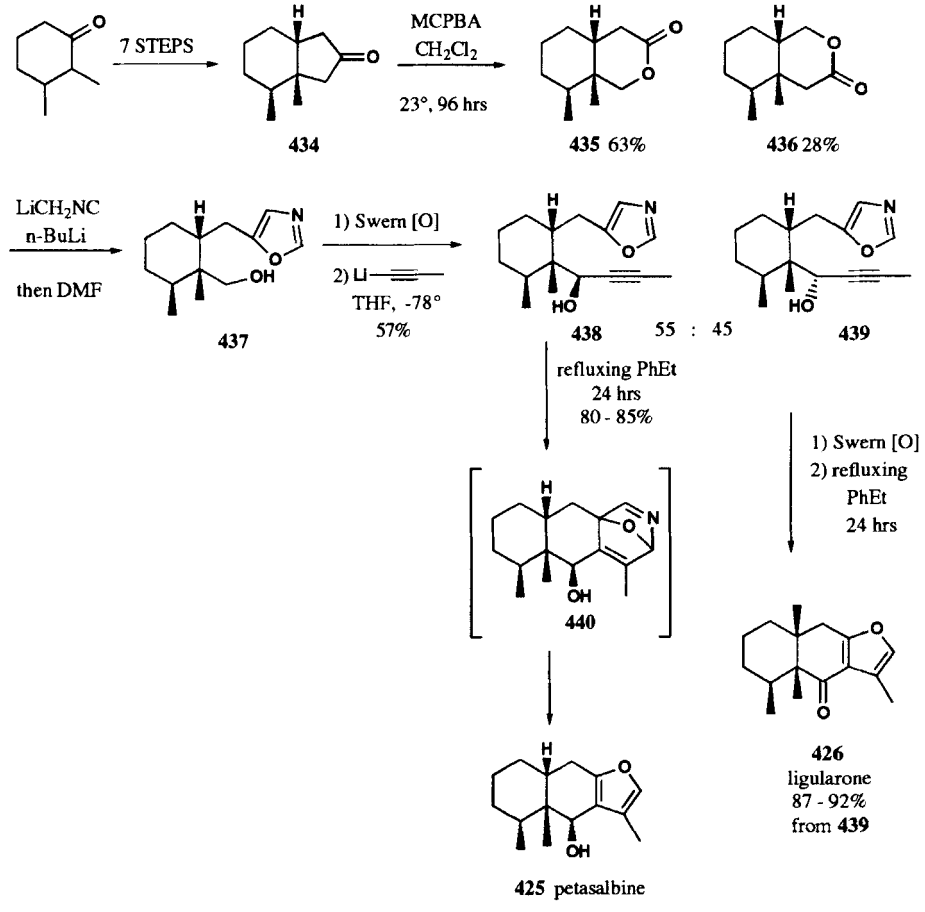
The eremophilane sesquiterpenes petasalbine (**425**)[130] and ligularone (**426**)[131] are representative rearranged sesquiterpenes which engendered a good deal of attention in the late 1970's. In particular, Yamakawa and Satoh described syntheses of several compounds in this class.[132] Because



Scheme 73. *Yoshikoshi Ligularone Synthesis*

ligularone is readily converted to petasalbine by Birch reduction,[133] a formal synthesis of the latter can be claimed when the former is produced. The two latest syntheses were designed to showcase technology for the annulation of 3-methylfuran rings. In both works, the relative stereochemistry was established using well-known intermediates and chemistry. Yoshikoshi[134] established the relative stereochemistry of the eremophilane ring system (Scheme 73) by methylcuprate addition to the known dione **427**[135] producing the desired arrangement in **428**. Wolff-Kishner reduction removed one carbonyl and introduction of another at the appropriate position required 7 steps from **428** giving **429.** Annulation of the furan began with conjugate addition of the diketone to unsaturated nitro compound **430** and ring closure with nitro group displacement producing the regioisomers **431** and **432.** Oxidative elimination of phenylsulfenic acid gave racemic ligularone and isoligularone,[136] respectively.

The Jacobi approach to 3-methylfuran synthesis[137] involves a novel cycloaddition of alkynes to oxazoles followed by *in situ* extrusion of HCN to cap an interesting and efficient process (Scheme 74). The known hydrindanone **434**[138] was produced in 7 steps from 2,3-dimethylcyclohexanone.

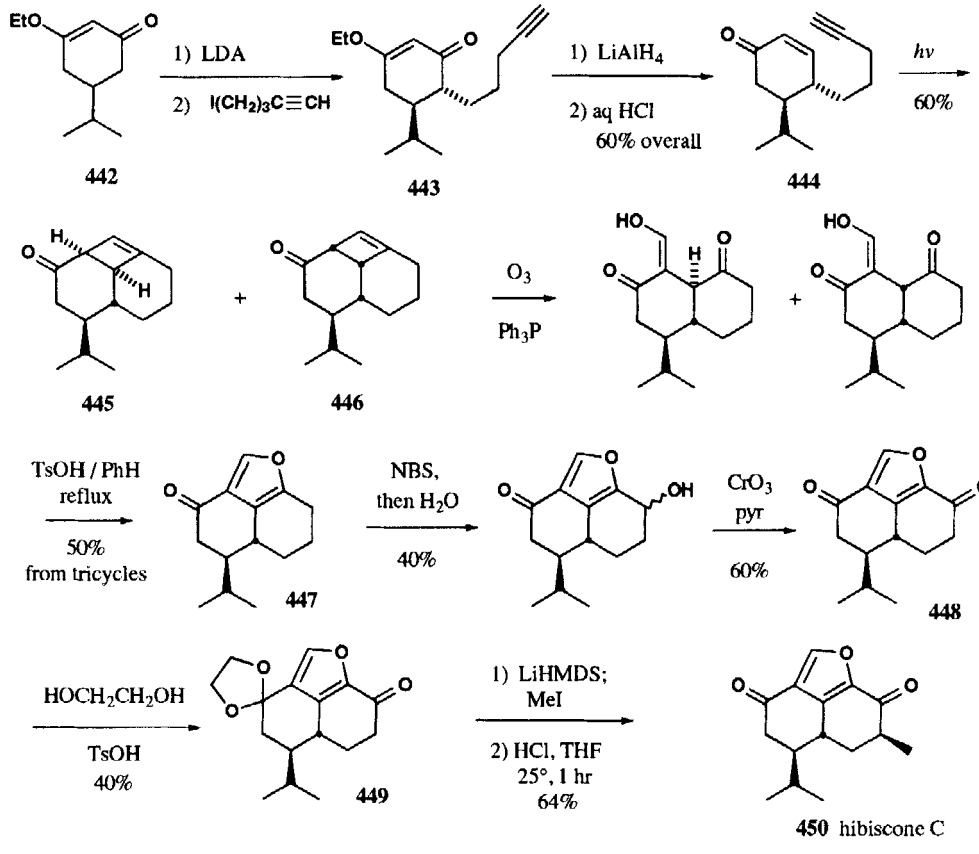


Scheme 74. *Jacobi Synthesis of Petasalbine and Ligularone*

establishing all of the relative stereochemistry. Baeyer-Villiger oxidation gave a mixture of the two regioisomers **435** and **436**. Separation of **435** and Schollkopf reaction using lithium methylisocyanide gave rise to the oxazole **437**. Oxidation to the aldehyde and addition of lithiopropyne gave a nearly 1:1 mixture of diastereomeric alcohols in 80-85% combined yield which could be separated. The required isomer (**438**) for petasalbine production was heated, giving rise to the intermediate [4+2] adduct (**440**) which underwent *in situ* cycloreversion with extrusion of HCN to give racemic petasalbine. Oxidation of **439** to the ketone was followed by heating to give racemic ligularone, completing a pleasing synthesis.

HIBISCONE C

Hibiscone C (**450**)[139,140] contains a furan ring fused on consecutive sides to a bicyclo[4.4.0] system. Smith assembled this substance relying on intramolecular alkyne-enone photocycloaddition (Scheme 75).[141] Alkylation of **442** gave alkyne **443**. Reduction and acidic rearrangement led to the



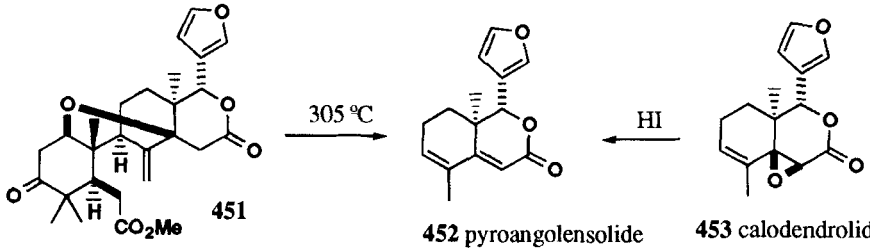
Scheme 75. *Smith Hibiscone C Synthesis*

key substrate **444**. Irradiation in hexane under argon for 24 hrs gave the isomeric photadducts **445** and **446** in a combined 60% yield. Ozonolysis and acidic cyclization led to the furan **447**. Oxidation gave

the diketone **448**, paving the way for introduction of the final carbon. Reaction of **448** with ethylene glycol and acid provided the monoprotected compound **449** which would be noteworthy, except for the fact that the yield is low and starting material and other ketalization products were obtained and recycled. Alkylation of the derived enolate with MeI installed the final stereocenter, with acidic deketalization providing hibiscone C.

DEGRADED LIMONOIDS

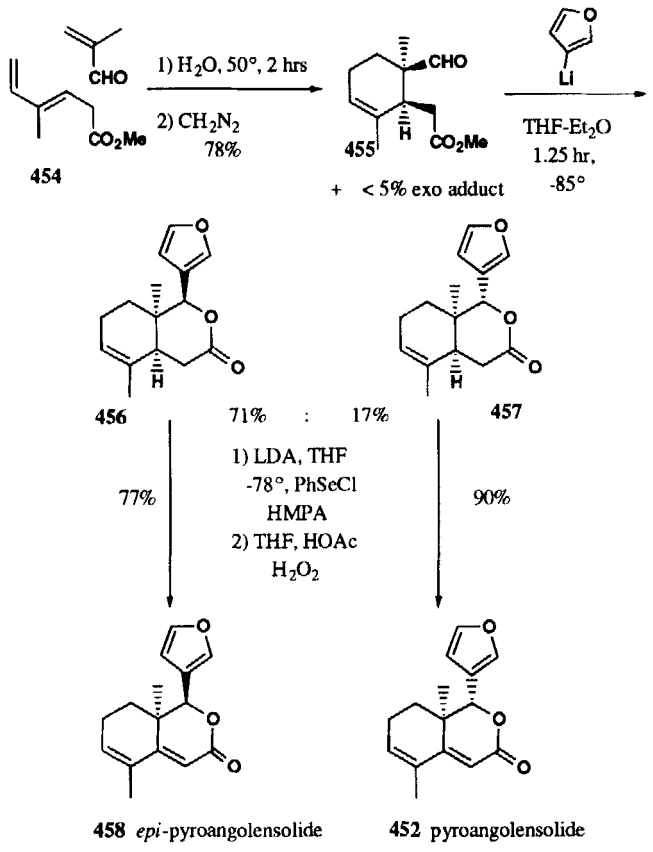
When the naturally occurring limonoid methyl angolensate (**451**) is pyrolyzed at 305°, pyroangolensolide (**452**) is produced, perhaps a result of consecutive β-elimination and



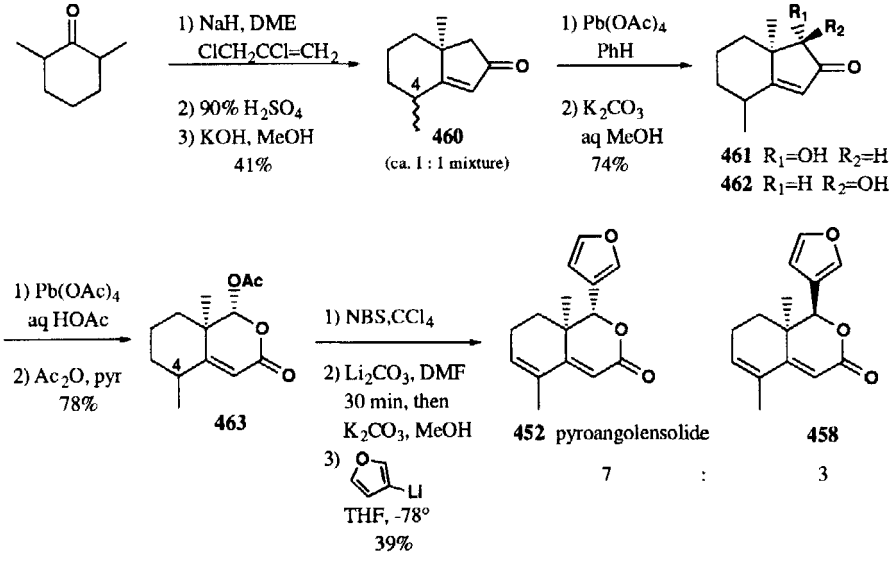
retro-ene processes.[142] Treatment of calodendrolide (**453**),[143] a naturally occurring limonoid degradation product with hydriodic acid also produces **453**. Tokoroyama and coworkers described eight step syntheses of pyroangolensolide and *epi*-pyroangolensolide in 1973,[144] although, some doubt remained as to the correct relative configuration of the isomers. The structural assignment was confidently made by Grieco in 1985 as a result of their syntheses of racemic **452** and **453** (Scheme 76).[145] Diels-Alder cycloaddition of methacrolein and diene **454** in water followed by re-esterification led to the *endo* adduct **455** in good yield along with a small amount of the *exo* adduct. Treatment with 3-furyllithium provided the lactones **456** and **457** in 71% and 17% yield respectively. Separation and olefin introduction using the selenoxide elimination provided two epimers with very similar ^{1}H NMR spectra. X-ray crystallographic analysis of the compound derived from the major isomeric product of the lactonization reaction revealed the structure to be **452**, confirming the structure of *epi*-pyroangolensolide as **458**. This confirmed the relative stereochemistry of calodendrolide as well.

Tokoroyama *et al.* has recently followed up a 1973 communication with a full account of their work (Scheme 77).[146] Wichterle annulation of 2,6-dimethylcyclohexanone provided the hydrindenone **460** after hydrolysis and aldol cyclization as a nearly equal mixture of diastereomers. Oxidation by $Pb(OAc)_4$ led to a diastereomeric mixture of α-hydroxyketones, with **462** being the major product as a result of equilibration during the base-induced acetate hydrolysis step. α-Cleavage with $Pb(OAc)_4$ and acetylation provided the lactone **463**, still as a mixture at C 4. Allylic bromination and elimination served to introduce the desired olefin regiospecifically. Acetate hydrolysis led to the penultimate lactol which was treated with 3-lithiofuran to give a mixture of pyroangelensolide and its epimer in a 7:3 mixture respectively. The isomers were separable by chromatography on silica.

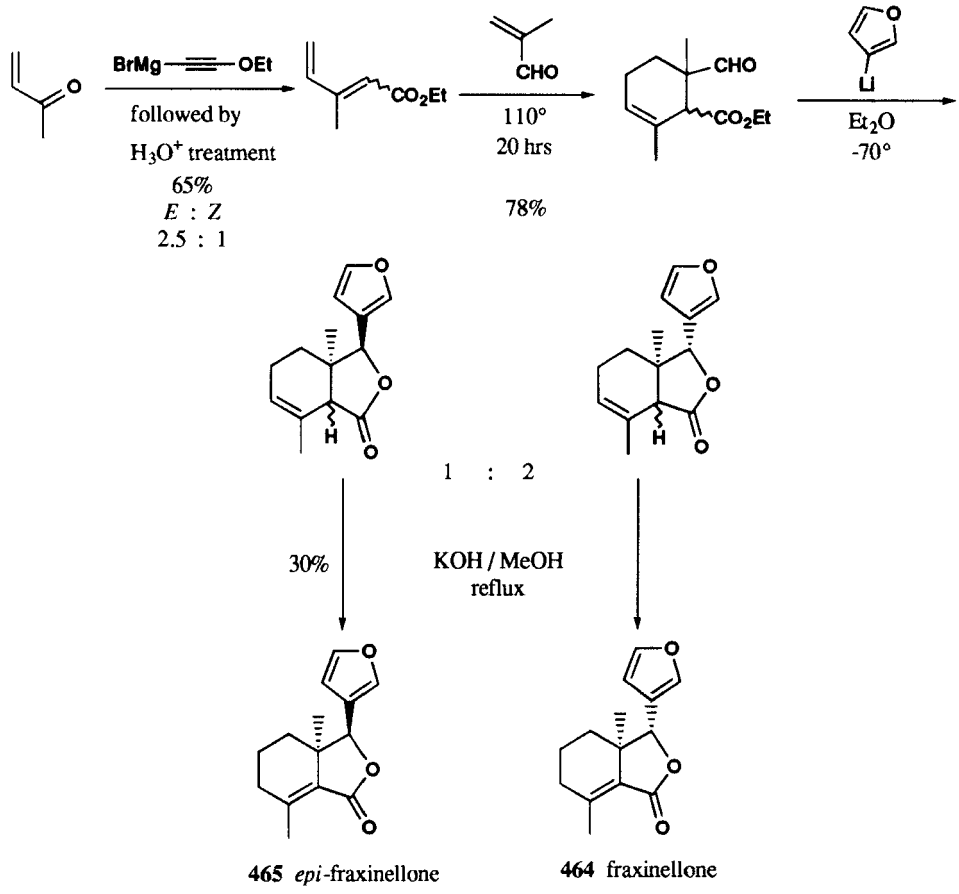
The degraded limonoids fraxinellone (**464**) and *epi*-fraxinellone (**465**)[147] are closely related to pyroangelensolide. Interestingly, a 1981 synthesis of fraxinellone by Tokoroyama (Scheme 77a)[148] is



Scheme 76. *Grieco Syntheses of Pyroangolensolide and epi-Pyroangolensolide*



Scheme 77. *Tokoroyama Synthesis of Pyroangolensolide*

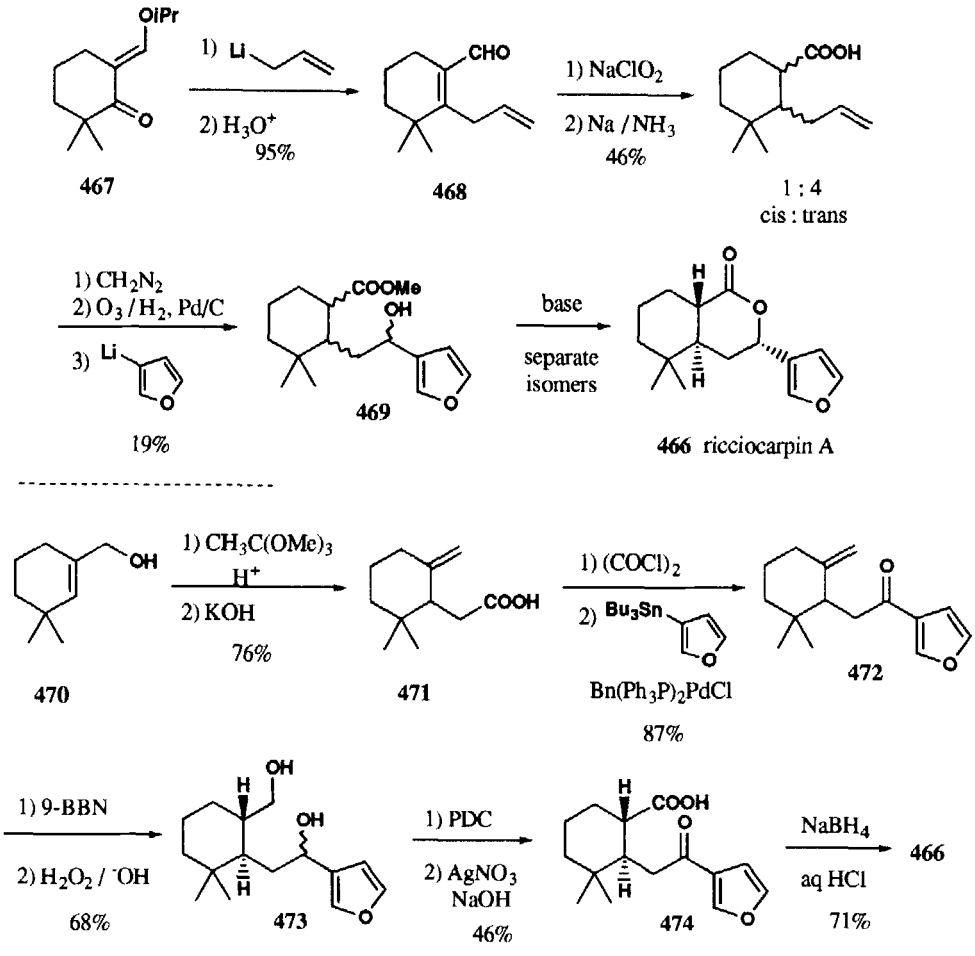


Scheme 77a. *Tokoroyama Syntheses of Fraxinellone and epi-Fraxinellone*

quite similar to the 1985 Grieco pyroangelensolide synthesis (Scheme 76). Although lacking in stereo-control, this four-step route reported the preparation of nearly a half gram of racemic **464**.

RICCIOCARPIN A

Ricciocarpin A (**466**) was isolated from the bryophyte *Ricciocarpos natans* and exhibited molluscicidal activity against the water snail *Biomphalaria glabrata*.[149] Two syntheses have appeared from the same laboratory (Scheme 78).[150] The first involves allyllithium addition to the unsaturated ketone **467** producing **468** after hydrolysis of the intermediate β-hydroxy enol ether. Oxidation to the acid and Birch reduction gave a 1:4 mixture of the *cis/trans* isomers in moderate yield. The mixture was carried on to the furanoester **469** which was cyclized and separated to give racemic ricciocarpin A, the result of a rather non-selective process. The second effort was somewhat more selective. Orthoester Claisen rearrangement of **470** gave the acid **471**. This was converted to the acid chloride and coupled with 3-tributylstannylfuran under catalysis by Pd(II) to give the 3-furylketone **472**.



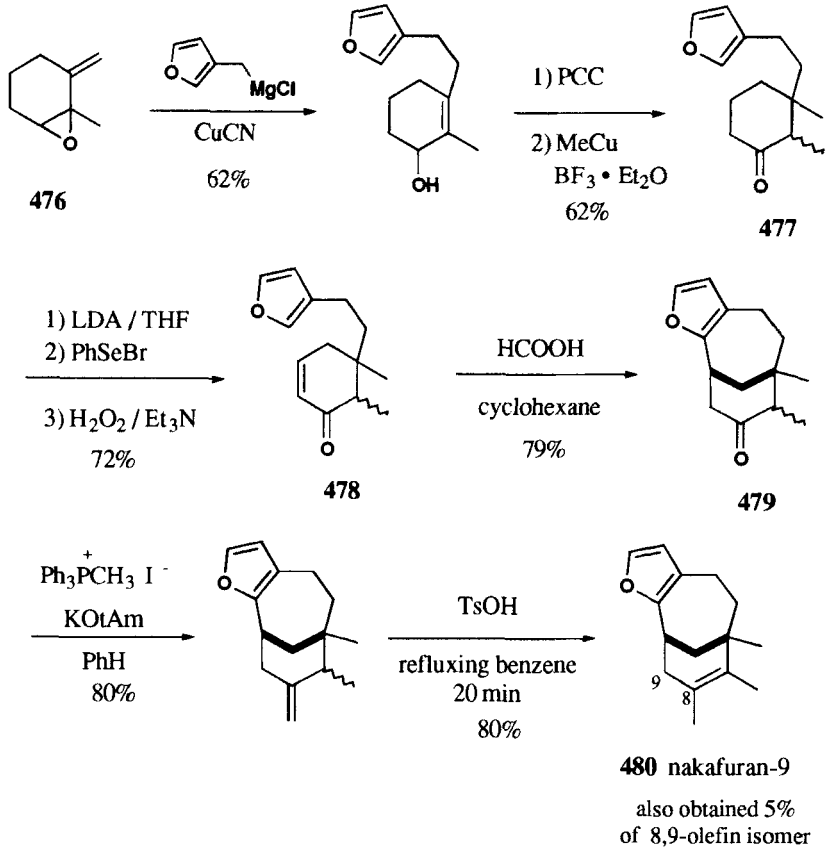
Scheme 78. *Zinsmeister-Eicher Syntheses of Ricciocarpin A*

Hydroboration-oxidation produced the *trans* isomer **473** in 68% yield. However, a chromatography was required and no other isomers were reported found. Oxidation to the keto acid **474** was followed by ketone reduction and lactonization to give racemic **466**, this time in 71% yield in the final step, but after a chromatography and a recrystallization. Note that ketone **472** has been isolated from the sponge *Dictyodendrilla cavernosa*[151] and was previously prepared as an intermediate in a synthesis of ancistrofuran by Baker.[70]

NAKAFURANS-8 AND -9

Nakafuran-8 (**489**) and -9 (**480**) have been isolated from marine sponges of the genus *Dysidea* and from the nudibranchs *Hypselodoris godeffroyana* and *Chromodoris maridadilus* which graze upon *D. fragilis*.[152] Both metabolites are fish antifeedants. Continuing a general study of furan-terminated cationic olefin cyclizations, Tanis[153] constructed the bridged bicyclic ring system of nakafuran-9

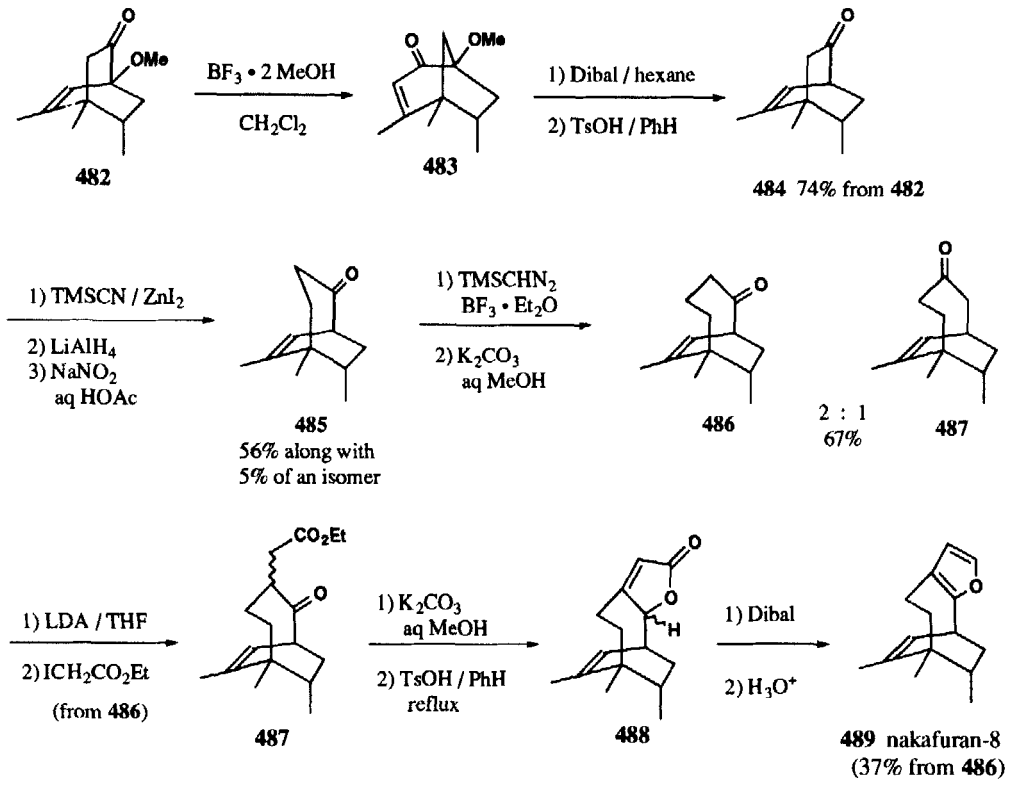
with an acid-promoted cyclization of an enone onto a pre-existing furan (Scheme 79). The synthesis began with the copper-catalyzed conjugate epoxide opening of **476** with 3-furylmagnesium chloride.



Scheme 79. *Tanis Synthesis of Nakafuran-9*

PCC oxidation and boron trifluoride assisted addition of methylcopper to the derived enone gave ketone **477** as a mixture of diastereomers. Selenylation of the kinetic enolate and selenoxide elimination in the presence of triethylamine suppressed premature cyclization and provided enone **478**. Treatment of **478** with formic acid in cyclohexane produced the bicyclo[4.3.1]decane **479** in 79% yield. After Wittig olefination and acid-catalyzed olefin isomerization, nakafuran-9 was obtained in a total of only 8 steps and an excellent 14% overall yield.

The synthesis of the isomeric nakafuran-8 by Yamamoto[154] (Scheme 80) took a much different course, involving 2 ring expansions. This approach involved formal reduction of a bridgehead methoxy substituent on Diels-Alder adduct **482**, sequential ring enlargements and construction of the furan moiety *via* butenolide reduction. Lewis acid-catalyzed rearrangement of readily available ketone **482** produced conjugated enone **483**. DIBAL reduction of the ketone and further rearrangement by treatment with TsOH gave ketone **484** in 74% yield. Tiffeneau-Demjanov ring expansion of

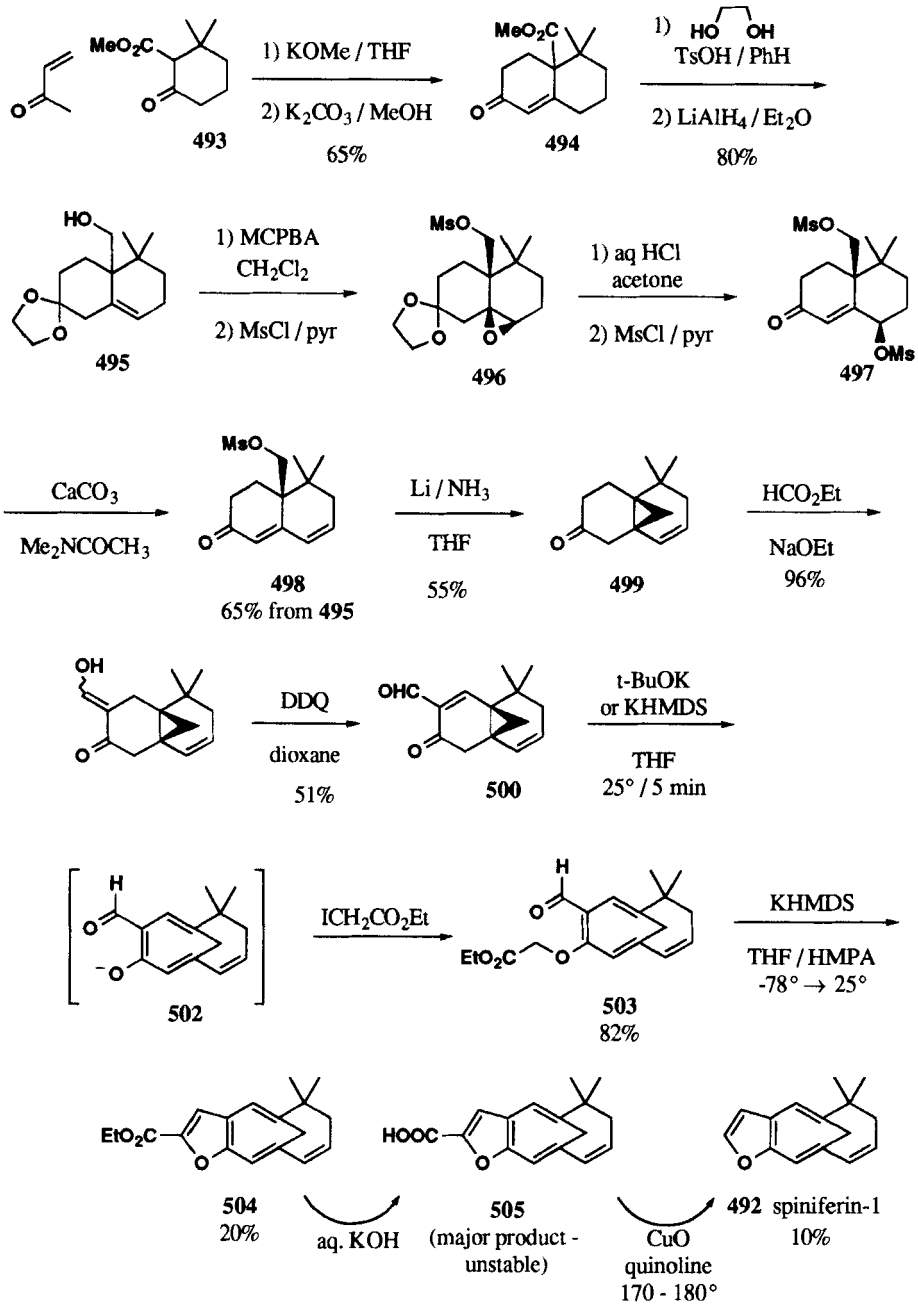


Scheme 80. *Yamamoto Synthesis of Nakafuran-8*

484 by sequential formation of the O-trimethylsilyl cyanohydrin, LAH reduction and treatment with nitrous acid gave **485**. A second ring enlargement is carried out by reaction of **485** with trimethylsilyl diazomethane and $BF_3 \cdot Et_2O$ to produce a mixture of two isomeric ketones in a 2:1 ratio. Alkylation of **486** with LDA and ethyl iodoacetate afforded a mixture of diastereomeric ketoesters **487** which were converted to butenolide **488** by saponification of the ester and treatment of the resulting ketoacid with TsOH. Reduction of the butenolide and dehydration produced nakafuran-8 over 12 steps and 7% overall yield.

SPINIFERIN-1

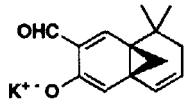
The Mediterranean sponge *Pleraplysilla spinifera* elaborates a number of terpenes. The most structurally unusual of these is spiniferin-1 (**492**), an unstable substance isolated in 1975 by Minale and coworkers.[155] It appears to be the first natural product isolated which contains the 1,6-methano[10]annulene carbon framework. The only synthesis of spiniferin-1 is that of Marshall[156] shown in Scheme 81. The key transformation in the synthesis is the introduction of the methanoannulene structural unit *via* a 6-electron electrocyclic ring opening. The synthesis began with Robinson annulation of the ketoester **493** with MVK to afford **494**. Protection of the ketone with concomitant



Scheme 81. *Marshall Synthesis of Spiniferin-1*

olefin migration and ester reduction gave **495**. Epoxidation and mesylation gave epoxide **496**. Hydrolysis and eliminative ring opening of the epoxide followed by mesylation provided **497**. Elimination of the mesylate to afford dienone **498** and Birch reduction with intramolecular trapping yielded the

cyclopropane **499** in 19% overall yield. Regiospecific formylation of **499** by Claisen condensation followed by careful dehydrogenation with DDQ yielded the key intermediate **500**. Enolization with t-BuOK or KHMDS gave rise to (presumably) the intermediate cross-conjugated dienolate **501** which



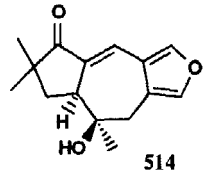
501

underwent electrocyclic ring opening to the cycloheptatriene **502** that was immediately trapped with ethyl iodoacetate to give ester **503**, thus avoiding isolation of the very unstable ketoaldehyde. In a fortuitous development, it was found that addition of base to aldehyde-ester **503** followed by acidification of the aqueous phase during extractive workup produces a mixture of ester **504**, spiniferin-1 carboxylic acid **505** and trace amounts of spiniferin-1. The yield of spiniferin-1 was increased by heating the unstable carboxylic acid **505** in quinoline with copper oxide to effect decarboxylation. Although the yields are low due to the instability of the product, spiniferin-1 was obtained in 0.75% overall yield in 15 steps.

V. COMPOUNDS WITH FURAN AND THREE RINGS

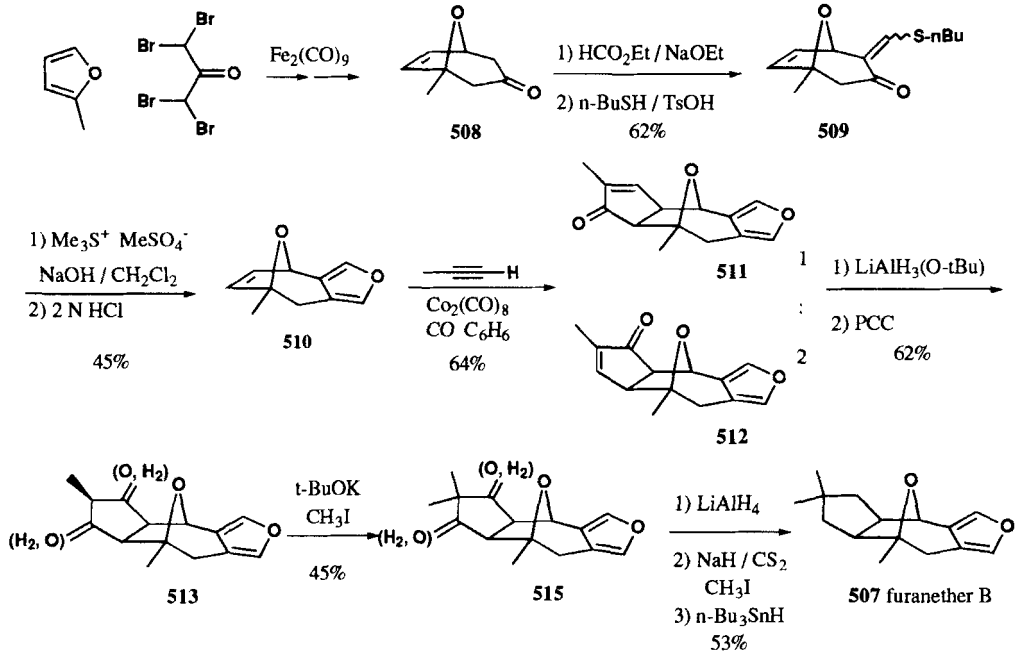
FURANETHER B

To date, only a single furanosesquiterpene in this structural class has been prepared. Schore has reported two strategically similar syntheses[157] of furanether B (**507**), a lactarane metabolite of the yellow mushroom *Lactarius scrobiculatis*.[158] Both routes utilize intermolecular Pauson-Khand reaction to establish the exo-fused cyclopentane ring. In the first approach (Scheme 82) oxyallyl cation-furan cycloaddition produced the oxabicyclo[3.2.1]octane system **508**. The furan ring was established by reaction of the *n*-butylthiomethylene derivative **509** with trimethylsulfonium methylide, giving an intermediate epoxide which was rearranged and aromatized with HCl in THF leading to **510**. Upon Pauson-Khand reaction the regioisomers **511** and **512** were produced in a 1:2 ratio respectively. Because of the local symmetry of the product, this mixture was of no consequence. Complete reduction of the enone system with $LiAl(Ot\text{-}Bu)_3H$ produced a mixture of alcohols which were oxidized back up to the ketones **513**. Methylation installed the final carbon in 45% yield, somewhat low due to competing ether bridge cleavage of one of the regioisomers giving **514** in addition to the desired **515**. A deoxygenation sequence converted the two regioisomers of **515** to racemic furanether B.



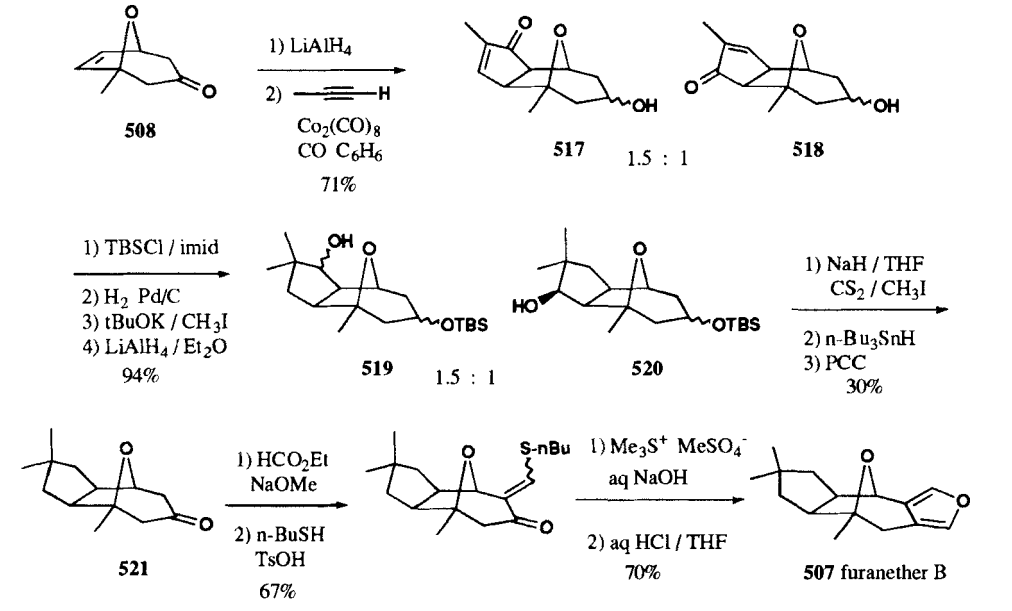
514

side product of alkylation (25%)



Scheme 82. *First Schore Synthesis of Furanether B*

The second route (Scheme 83) differed only in the substrate used in the timing of the furan and cyclopentane ring annulations. The carbonyl group of **508** was reduced and the cyclopentenone



Scheme 83. *Second Schore Synthesis of Furanether B*

was appended, again with an inconsequential lack of regioselectivity providing **517** and **518**. Functional group manipulation and methylation led to the isomers **519** and **520**, which underwent deoxygenation merging to compound **521**. In this case, the troublesome elimination noted in the previous route was not observed. At this point, the bias provided by the bridgehead methyl group allowed regiospecific annulation of the furan as before leading to furanether B.

VI. CONCLUSION

Although there has been quite a lot of activity in this area recently, most of the work has been geared to the production of specific natural products. Very little general methodology has been developed to be specifically applied to the synthesis of furanosesquiterpenes. This is probably because there is large structural variation within the class, despite the fact that the metabolites are limited to only 11 non-furan carbons. As expected, the simpler members of the class have been synthesized more frequently than the more complex ones, although none of the compounds so far produced by synthesis can be deemed to be of "high" or unusual complexity.

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