1990

Approaches to terpenoid natural products using reactive intermediates

Steven Barse Laramay
Iowa State University

INFORMATION TO USERS

The most advanced technology has been used to photograph and reproduce this manuscript from the microfilm master. UMI films the text directly from the original or copy submitted. Thus, some thesis and dissertation copies are in typewriter face, while others may be from any type of computer printer.

The quality of this reproduction is dependent upon the quality of the copy submitted. Broken or indistinct print, colored or poor quality illustrations and photographs, print bleedthrough, substandard margins, and improper alignment can adversely affect reproduction.

In the unlikely event that the author did not send UMI a complete manuscript and there are missing pages, these will be noted. Also, if unauthorized copyright material had to be removed, a note will indicate the deletion.

Oversize materials (e.g., maps, drawings, charts) are reproduced by sectioning the original, beginning at the upper left-hand corner and continuing from left to right in equal sections with small overlaps. Each original is also photographed in one exposure and is included in reduced form at the back of the book.

Photographs included in the original manuscript have been reproduced xerographically in this copy. Higher quality 6" x 9" black and white photographic prints are available for any photographs or illustrations appearing in this copy for an additional charge. Contact UMI directly to order.

U·M·I

University Microfilms International
A Bell & Howell Information Company
300 North Zeeb Road, Ann Arbor, MI 48106-1346 USA
313/761-4700 800/521-0600

Order Number 9085089

Approaches to terpenoid natural products using reactive intermediates

Laramay, Steven Barse, Ph.D.

Iowa State University, 1990

U·M·I
300 N. Zeeb Rd.
Ann Arbor, MI 48106

Approaches to terpenoid natural products using reactive intermediates

by

Steven Barse Laramay

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

Department: Chemistry
Major: Organic Chemistry

Approved:

Signature was redacted for privacy.

In Charge of Major Work

Signature was redacted for privacy.

For the Major Department

Signature was redacted for privacy.

For the Graduate Office

Iowa State University
Ames, Iowa

1990

TABLE OF CONTENTS

DEDICATION

This manuscript is dedicated to the memory of my late grandmother Helen Smith Barse who had the greatest influence in my education.

GENERAL INTRODUCTION

The goal of a synthetic organic chemist is not only the synthesis of complex natural products, but also to synthesize these products using novel methodology and to develop a concise, efficient route. A problem that one learns while developing an approach is that the first route rarely works, so one must be ready to adapt to the inevitable stumbling blocks that lie in the original approach. The purpose of this research was to develop convergent routes to natural products that contain [3.2.1] bicyclic ring systems. What will be shown is the evolution of these approaches toward that goal. Part I describes an approach to kaurenoid natural products using bridgehead enone Diels-Alder methodology to synthesize the tetracyclic carbon framework. Part II describes a conceptually different approach to kaurenoid natural products. Finally, Part III describes an approach to trixikingolides natural products using bridgehead carbocation methodology.

EXPLANATION OF THESIS FORMAT

This thesis is written so that each section can be regarded as a separate article in publishable form. Therefore, the numbering of the figures, schemes, tables, and references is independent in each section.

PART I: AN ATTEMPTED APPROACH TO KAURENOID NATURAL PRODUCTS USING A BRIDGEHEAD ENONE DIELS-ALDER REACTION

INTRODUCTION

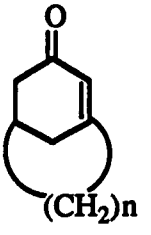
This manuscript will outline the synthetic program directed toward the synthesis of kaurenoid natural products. The proposed route would allow a convergent synthesis that starts with the bicyclic unit intact. Previous syntheses of this class of natural products used linear approaches that usually synthesized the bicyclic unit late in the synthesis. Our attempts used a bridgehead enone Diels-Alder reaction to construct advanced intermediates in our synthesis.

HISTORICAL

Unsaturation at a bridgehead position was long considered an unrealizable intermediate because of the strain that would be inherent in a compound such as **1**. Compound

1

1 can not conform to a 120° bond angle needed for the classic carbon - carbon double bond. Recently two comprehensive reviews by Warner,[1] and Kraus and coworkers[2] have appeared that discuss reactive bridgehead intermediates. Bridgehead enones (**2**) could play

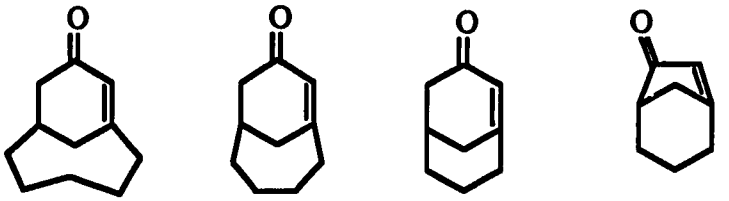


2

an important role in organic synthesis because of their high reactivity. Bridgehead enones would allow for the construction of quaternary carbons. Because of the constraints of the ring system, reactions could be highly stereospecific.

The classical study of [n.3.1] bridgehead enones is attributed to reports by House and coworkers in the late 1970s and early 1980s.[3-8] House and coworkers have synthesized a

variety of bridgehead enones including the bicyclo [5.3.1] undecenone **3**,[6] bicyclo [4.3.1] decenone **4**,[4] bicyclo [3.3.1] nonenone **5**,[3,5,8] and bicyclo [3.2.1] octenone **6**



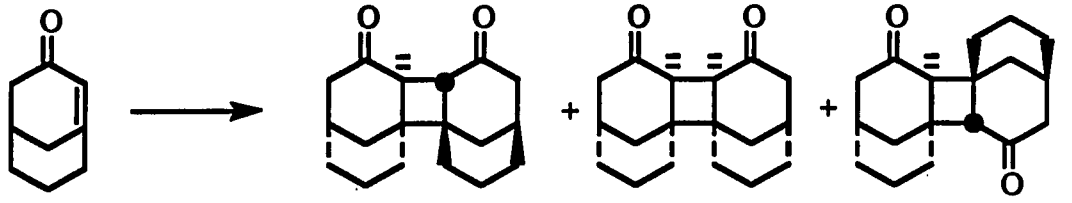
3 **4** **5** **6**

and studied the stability and reactivity of these compounds. House found that as the ring size decreased the reactivity of the enone increased. This is a result of the increasing strain of the double bond, thereby forcing the double bond to twist from planarity. Using Allinger's MMP1 molecular mechanics program, House has determined the average twist of the double bond and the inherent strain of each of the bicyclic systems (Table I).[7] These

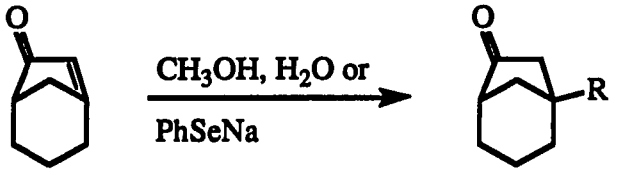
Table I. Selected Theoretical Data for Brigdehead Enones

Enone	average twist of C=C bond (°)	inherent strain (Kcal / mol)]
3	4	16.9
4	14	17.7
5	21	21.3
6	36	32.3

theoretical results coorelate well with the experimental results. Whereas enones **3** and **4** can be isolated in the absence of nucleophiles and show no propensity to dimerize upon heating, enones **5** and **6** can not be isolated. If there is no nucleophile present, enone **5** undergoes a facile [2 + 2] dimerization. The *in situ* generation of enone **5** produced three adducts **7**, **8**, and **9**.[5] Enone **6**, like **5**, undergoes facile 1,4 - additions in the presence of a variety of nucleophiles, such as methanol, water and sodium phenylselenide.[7] House



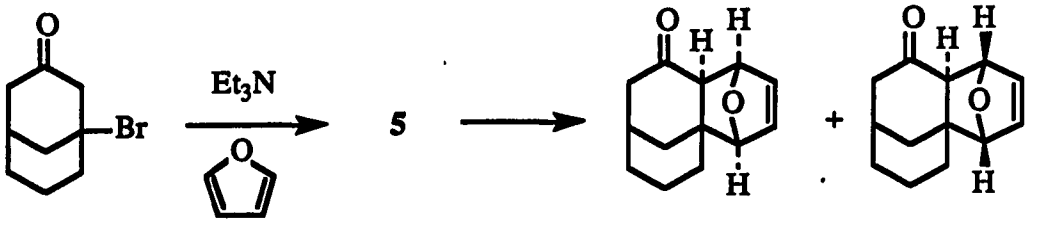
5 **7** (57 %) **8** (18) **9** (5 %)



6

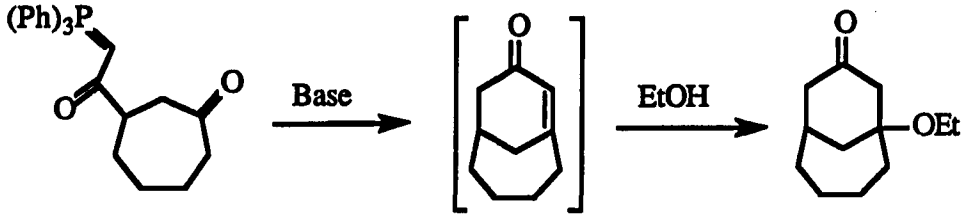
10 R = OCH_3
11 R = OH
12 R = SePh

and coworkers have also shown that enones **5** and **6** undergo facile [4 + 2] cycloaddition with furan at ambient temperature. Enone **5** produced both the exo adduct **13** (as the major product) and the endo adduct **14** (as the minor product) in the Diels-Alder reaction.[5] Recently Campbell and coworkers proved the existence of enone **5** by preparing enone **5** by flash vacum pyrolysis, and enone **5** was stable in solution at - 78 °C.[9]

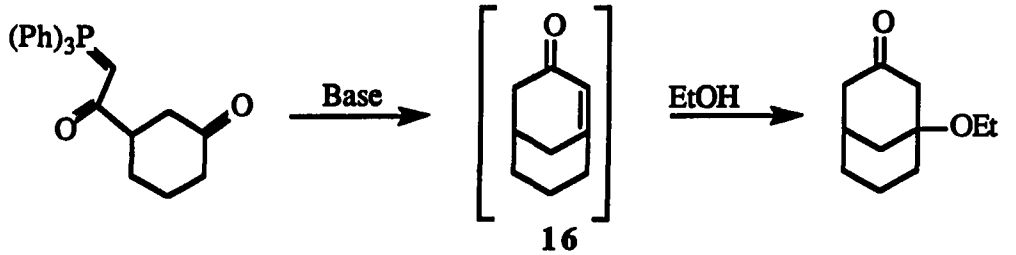


13 14

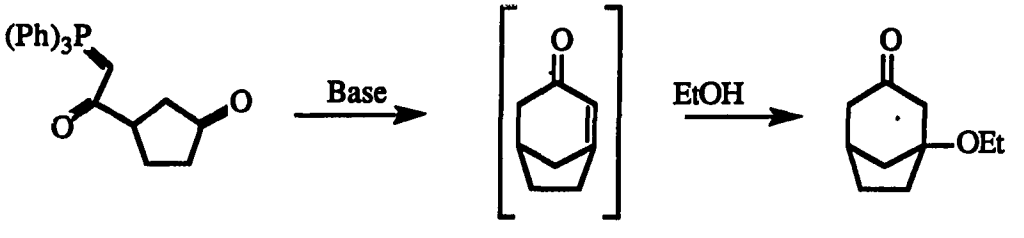
Bestmann and Schade have also been successful in preparing bicyclo [4.3.1] decenone **15**, bicyclo [3.3.1] nonenone **16**, and bicyclo[3.2.1] octenone **17** via



15



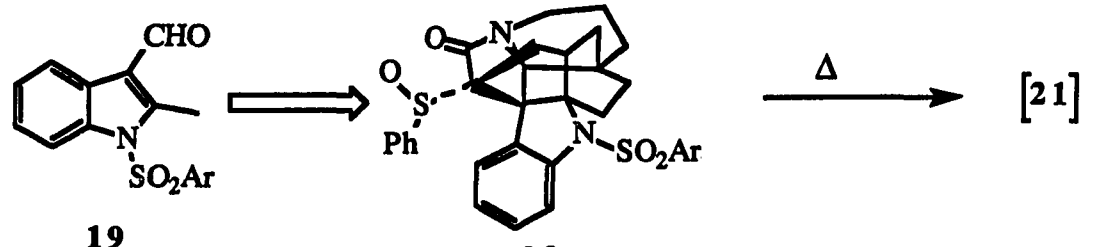
16



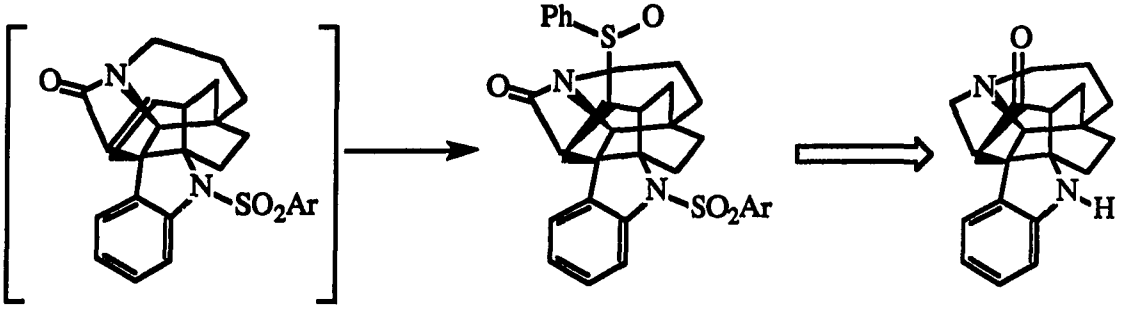
17

intramolecular Wittig reactions.[10] These bridgehead enones were trapped with ethanol to give bridgehead ethers.

The use of bridgehead enones as electrophiles has increased in recent years. Magnus and coworkers were the first to report the synthetic utility of bridgehead enones.[11] In their elegant synthesis of (±)-kopsanone (**18**), they used the high reactivity of bridgehead enones to effect a facile 1,2 - shift of phenylsulfenic acid. Starting with aldehyde **19** they were able to convert **19** to the sulfoxide **20**, which upon heating eliminated the phenylsulfenic acid to provide the bridgehead enone **21**. The resulting phenylsulfenic acid added across the enone to form the sulfoxide **22**. Sulfoxide **22** was then converted in three steps to (±)-kopsanone.

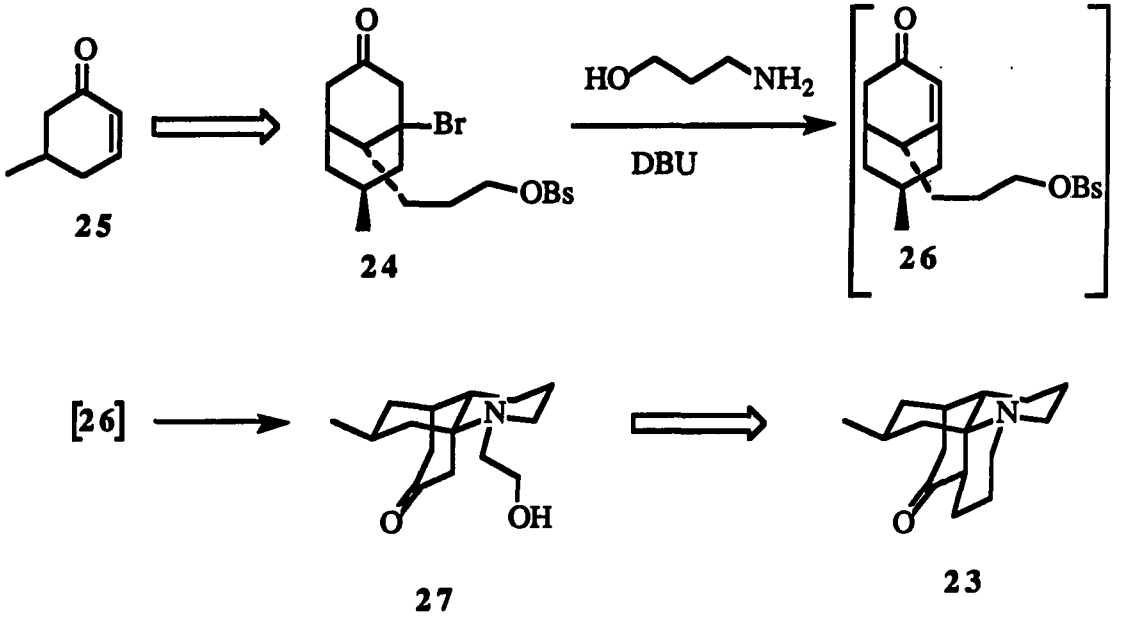


19 **20**

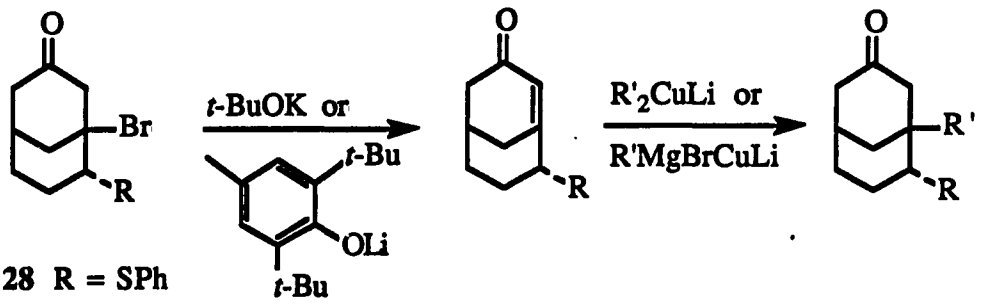


21 **22** **18**

Kraus and Hon also successfully employed a bridgehead enone in one of their two short approaches to (±)-lycopodine **23**.[12] The bridgehead enone was generated *in situ* by a dehydrohalogenation reaction of the bridgehead bromide **24**. Compound **24** was formed in seven steps from **25**. The enone **26** was generated by the addition of 1,8-diazobicyclo [5.4.0] undec-7-ene (DBU) and was then trapped with 3-amino-1-propanol to give **27**. Ketone **27** has been previously converted to lycopodine in two steps by Heathcock et al.[13]



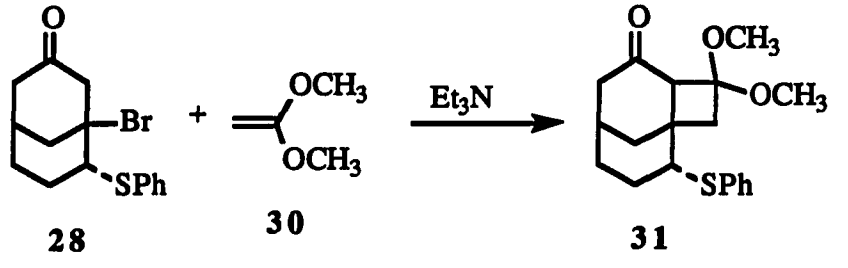
Kraus and Yi have also been successful in adding cuprates to *in situ* generated bridgehead enones.[14] A variety of cuprates such as methyl, vinyl, and phenyl have added 1,4 in greater than 50% yield to bridgehead enones derived from bromides **28** or **29**. Either potassium *t*-butoxide or lithuim 2,6-di-*t*-butyl-4-methylphenoxide was used as the base. This methodology allows for the alkylation at a bridgehead position.



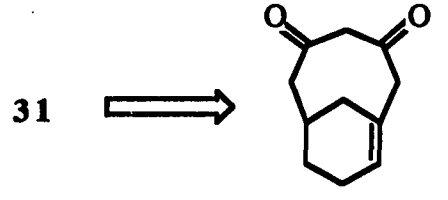
28 R = SPh

29 R = H

Kraus and coworkers have also reported the synthetic utility of the [2 + 2] addition of electron rich alkenes to bridgehead enones.[15] In the reaction of bridgehead bromide **28** and 1,1-dimethoxyethene **30** in the presence of triethylamine, adduct **31** was formed in 100% yield. After reduction followed by deacetylation, diketone **32** was formed. This diketone was proposed to be a key intermediate in the synthesis of the taxane class of natural products.



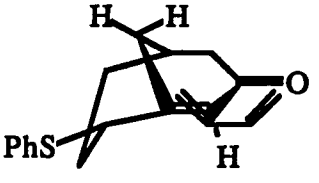
28 **30** **31**



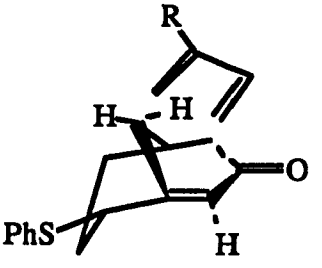
32

A systematic study of the potential of bicyclo [3.3.1] nonenones as dienophiles has been completed by Kraus and coworkers.[16, 17] In this study it was determined that a variety of dienes formed exclusively exo Diels-Alder adducts when excess triethylamine was added to a solution of the bridgehead bromide and 2 to 4 equivalents of the diene (Table II). It is important to note that 1,1-3-trisubstituted dienes (entries 5, 6, and 7) which are usually unreactive in the Diels-Alder reaction gave satisfactory yields of Diels-Alder adducts. The identity of the adducts were proven by using 2D NMR COSY and NOESY techniques on the adduct in entry 5 Table II.

Kraus has proposed transition state **33** as the rationale for the exclusive formation of the exo adduct.[17] In normal Diels-Alder reactions, the endo products are favored due to favorable secondary orbital overlap interactions,[18] but in this case the endo transition state **34** is sterically congested. The secondary orbital overlap interaction can not be attained; therefore, the less sterically demanding transition state **33** determines the stereochemical course of the reaction. Kraus has also suggested that the mechanism may not be concerted

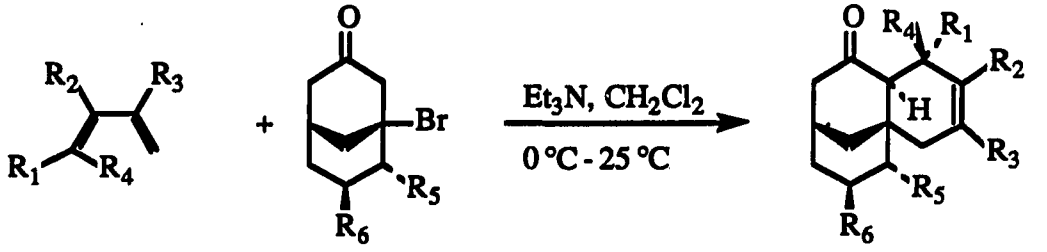


33



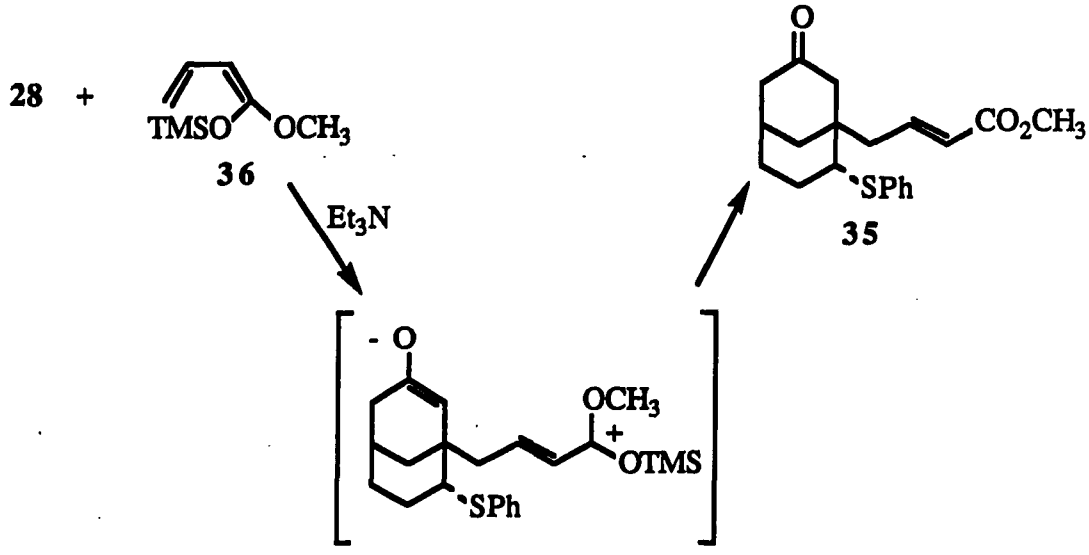
34

Table II. Reported Deils-Alder Reactions with Bridgehead Enones



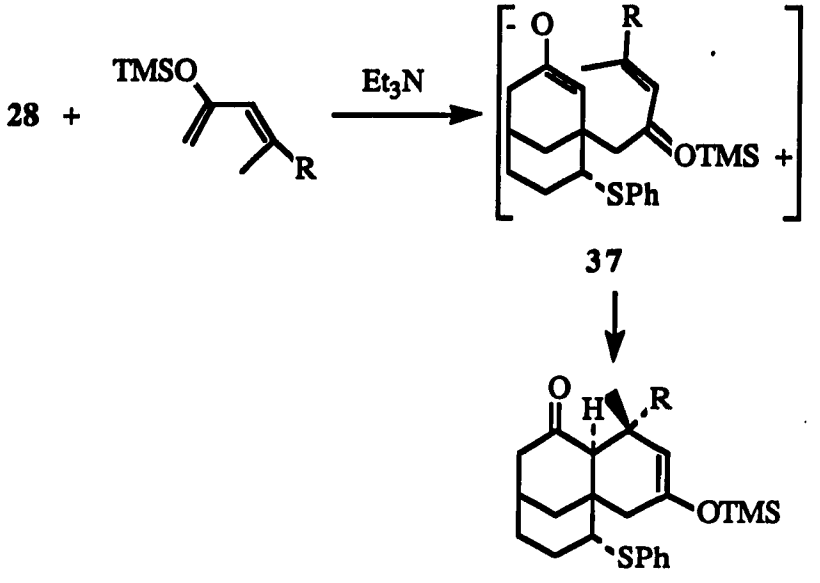
Entry	R_1	R_2	R_3	R_4	R_5	R_6	% yield
1	$(CH_2)_4$		OTMS	H	SPh	H	97
2	$(CH_2)_4$		OTMS	H	H	CH_3	52
3	(CH2)4		OTMS	CH_3	H	CH_3	-
4	OTMS	H	OCH_3	H	SPh	H	98
5	OTMS		H	CH_3	SPh	H	46
6	OTMS		H	CH_3	SPh	H	81
7	OTMS	CH3	H	CH_3	SPh	H	46

and that an ionic or polarized transition state may be more appropriate. The possibility of an ionic mechanism was supported since the α–β unsaturated ester **35** is the sole product formed in the reaction of diene **36** with the bridgehead enone derived from **28**.[17] Kraus

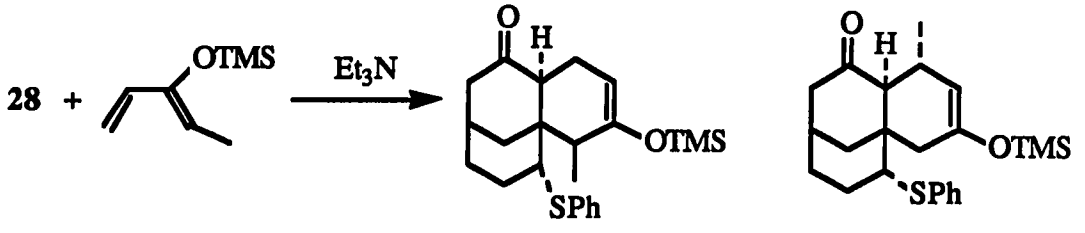


has proposed that this type of mechanism would also produce exclusively exo adducts by minimizing steric interactions in the intermediate **37**. Kraus and Liras have also reported further evidence of an ionic mechanism in the report of the inverse selectivity of diene **38** in the bridgehead enone Diels-Alder reaction.[19] The adduct **39** is the only adduct that was detected, and was the expected product from an ionic mechanism. Liras has since reported the bridgehead Diels-Alder reaction using diene **40**.[20] This diene was reported as the definitive test for the ionic mechanism, since products of a cyclopropyl- carbinyl cation rearrangements were expected if an ionic mechanism was involved. The only product

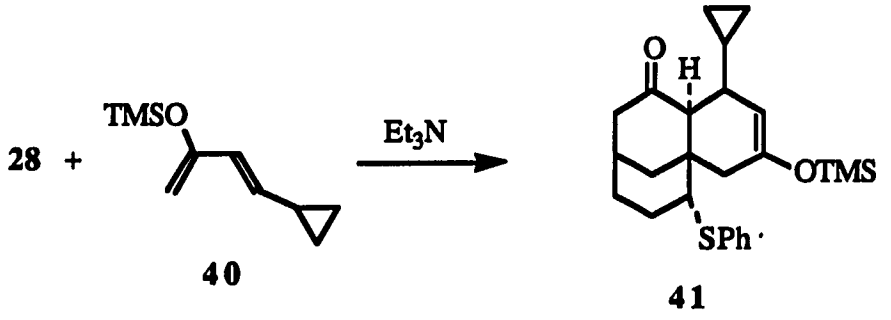
detected was adduct **41**, which has led Kraus to propose a polarized rather than an ionic or a concerted mechanism for the bridgehead enone Diels-Alder reaction.



37



39



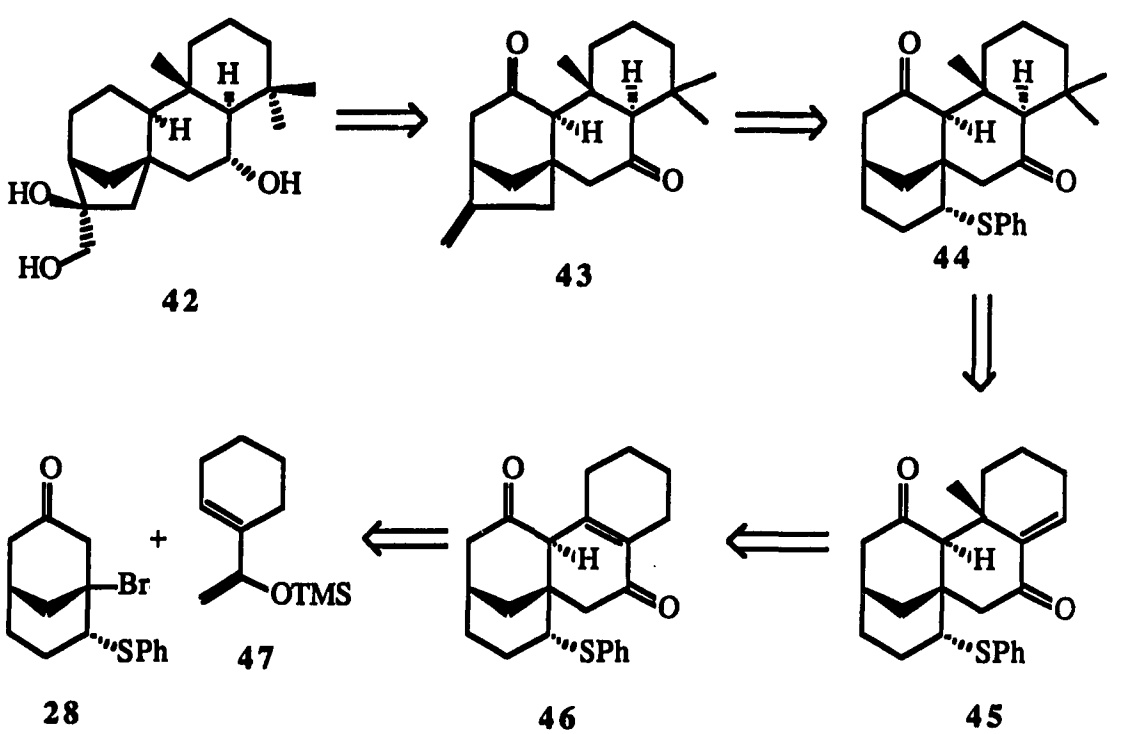
40

41

RESULTS AND DISCUSSION

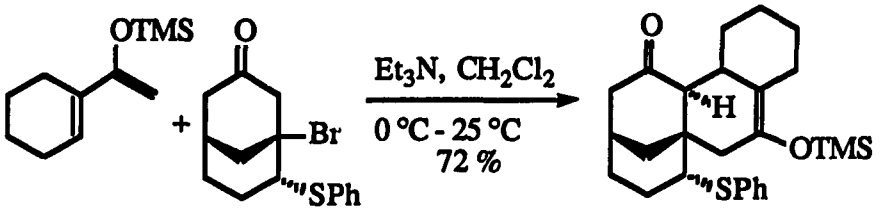
The key to our approach centered around the use of a bridgehead enone Diels-Alder reaction to construct the tetracyclic ring system. This approach would allow for a convergent synthesis if an appropriate diene was used and would allow for a synthesis that contains a latent bicyclo [3.2.1] octane ring system early in the synthesis. The retro-synthetic analysis of the approach to corymbol 42[21] is depicted in Scheme I. Corymbol will be synthesized from intermediate **43** by known functional group manipulations.

Scheme I



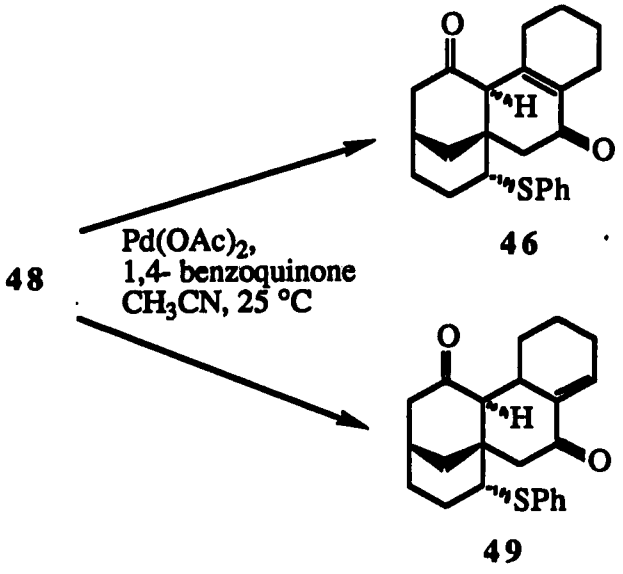
Ketone **44** will be formed from **43** by a previously reported ring contraction.[22] This ring contraction involves oxidation of the sulfide to the sulfoxide followed by elimination. The alkene is oxidation to the dialdehyde, then intramolecular aldol condensation to form a ring contracted unsaturated aldehyde. This aldehyde is reduced to the **43**. An iterative methyl cuprate addition was envisioned to transform **45** to **44**. Enone **45** will be synthesized by chlorotrimethylsilane assisted methyl cuprate addition to **46** followed by oxidation to the enone. Enone **46** is then synthesized by a bridgehead enone Diels-Alder reaction between the bridgehead bromide **28** and diene **47**, followed by oxidation to the enone.

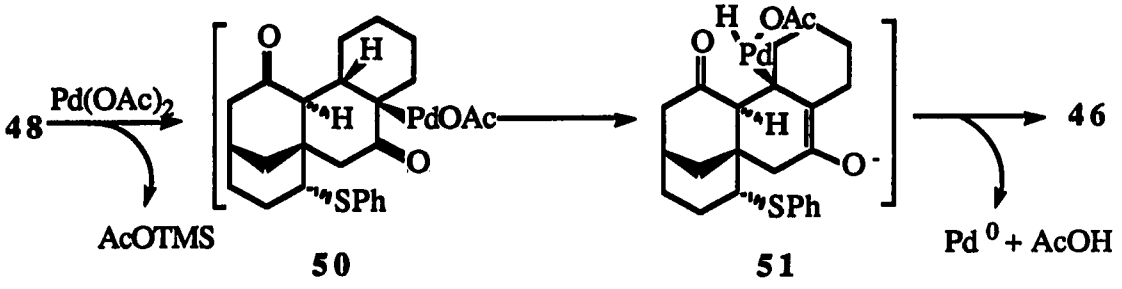
Our first goal was the synthesis of the tetracyclic enone **46** from the bridgehead bromide and the previously reported diene **47**.[23] The bridgehead enone Diels-Alder reaction with the bridgehead bromide **28** and diene **47** yielded the Diels-Alder adduct **48**



47 **28** **48**

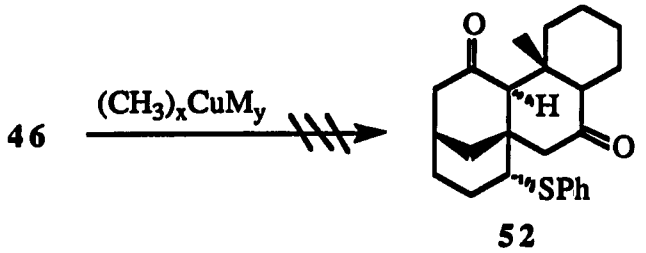
in 70% yield as the only diastereomer. The next task was the oxidation of the enol silyl ether to an enone. A Saegusa reaction [$Pd(OAc)_2$, 1,4-benzoquinone][24] was used to regioselectively oxidize **48** to the needed enone **46**. Two possible enones **46** and **49** could be formed. Enone **46** is the only isomer formed because of nonbonded interactions with the β-phenylthio group (PhS) only allowing intermediate **50** to form. The cis addition across the C - H bond occurs regioselectively to the weaker tertiary C - H bond



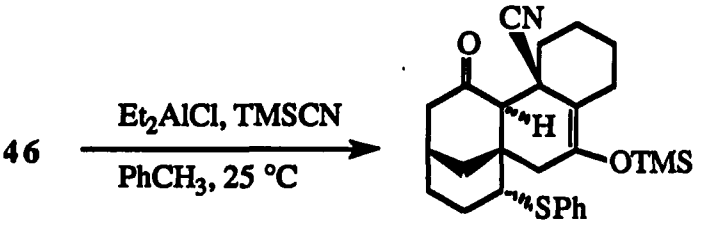


giving the intermediate **51** which eliminates to enone **46** as the sole product.

With the enone in hand, the next objective was the addition of the C - 10 angular methyl group (kaurene numbering) to form **52**. Several methyl cuprate reagents, such as

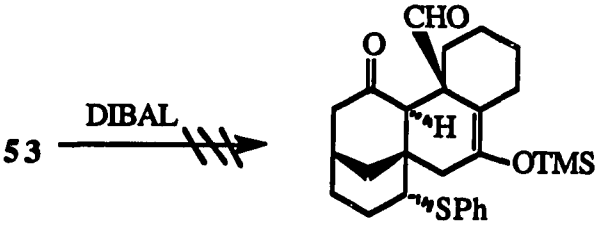


heterocuprates,[25] boron trifluoride etherate assisted cuprates,[26] and chlorotrimethylsilane assisted cuprates,[27] were employed to add to the enone, but all attempts failed. One group that did add to the enone was a cyano group. Using the conditions of Utimoto and coworkers (diethyl aluminum chloride and trimethylsilyl cyanide)[28] the nitrile **53** was

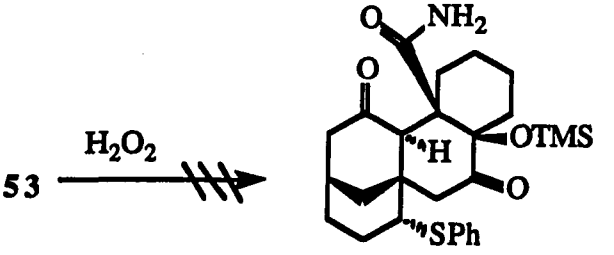


53

produced efficiently. Nitrile **53** was not able to be reduced to aldehyde **54** with diisobutyl aluminum hydride (DIBAL),[29] nor could it be oxidized to the peroxyimidic acid using hydrogen peroxide.[30] The later reaction could have led to the amide **55**. The failure of

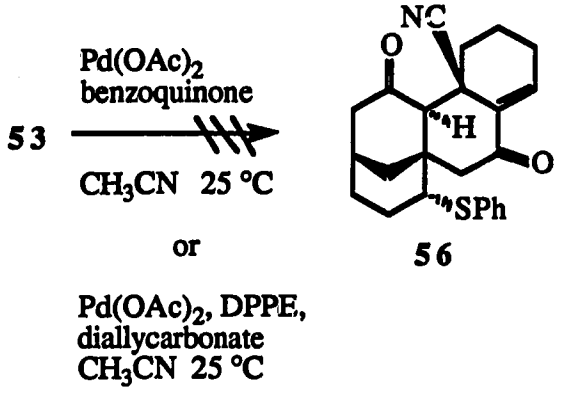


54



55

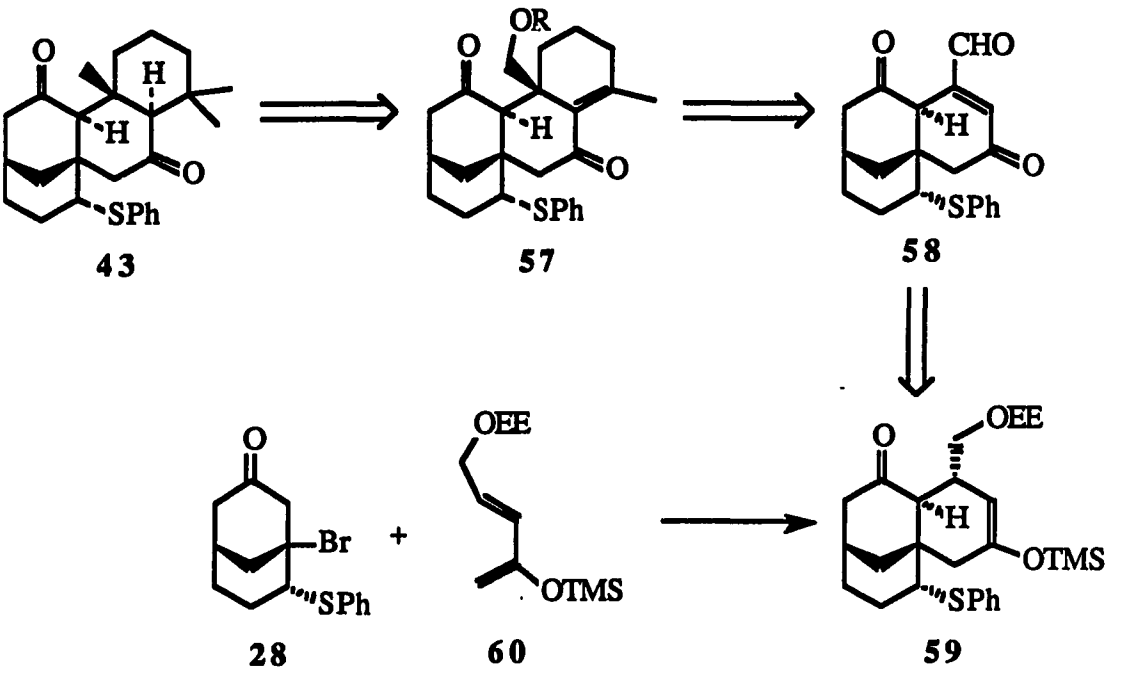
these reactions was attributed to a steric effect due to nonbonded interactions between the cyano group and the axial hydrogen at C - 4 (kaurene numbering). If the enol silyl ether could be oxidized to enone **56**, the non-bonded interaction would be minimized. First the Saegusa reactions conditions were attempted, but these conditions failed to provide enone **56**. There had been a report by Minami and coworkers[31] of the success of oxidizing enol silyl ethers to enones using $Pd(OAc)_2$, diallyl carbonate, and 1,2-bis(diphenylphosphino)-ethane. These conditions were also unsuccessful in oxidizing **53** to **56**.



Because of the difficulty in transforming the cyano group to the angular methyl group, a strategy to **43** was devised which would allow the addition of the angular methyl group as part of the diene. A tricyclic precursor would be formed in the bridgehead Diels-Alder reaction instead of a tertracyclic precursor. The fourth ring would be annulated later in the synthesis. This strategy is outlined in Scheme II. Enone **57** would allow for the synthesis of the geminal dimethyl group by a methyl cuprate addition. Enone **57** would be prepared by a Diels-Alder reaction between enone **58** and piperylene followed by isomerization of the double bond. Enone **58** would be synthesized from the bridgehead Diels-Alder adduct **59** by oxidation to the enone, deprotection of the ethoxy ethyl ether,

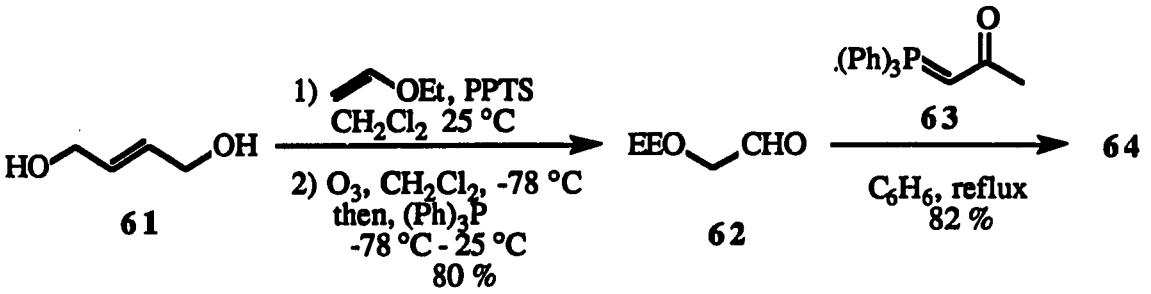
then oxidation of the allylic alcohol to the aldehyde. Adduct **59** would be prepared by a bridgehead enone Diels-Alder reaction between bridgehead bromide **28** and diene **60**.

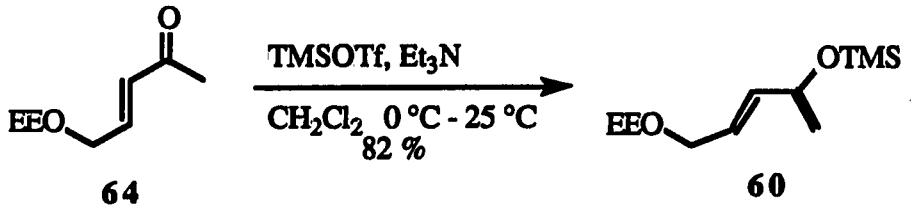
Scheme II

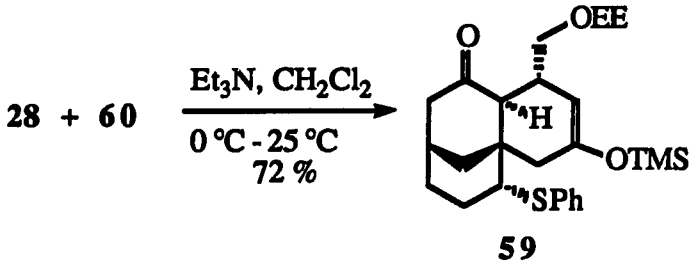


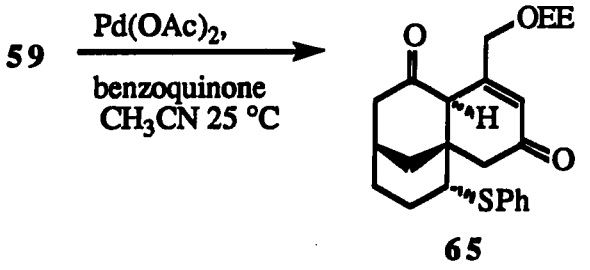
The diene **60** is prepared in four steps from 2-butene-1,4-diol (**61**). Protection of the diol as the diethoxyethyl ether was followed by ozonolysis which produced the protected hydroxy acetaldehyde **62**. Aldehyde **62** was transformed to diene **60** by a Wittig reaction with the keto phosphonate **63**[32] to form enone **64**, followed by reaction of the resulting enone with trimethylsilyl triflate (TMSOTf) and triethylamine, formed diene **60**. The bridgehead enone Diels-Alder reaction with the bridgehead bromide **28** and 1.2 equivalents of diene **60** produced the Diels-Alder adduct **59** as a single diastereomer. This adduct was

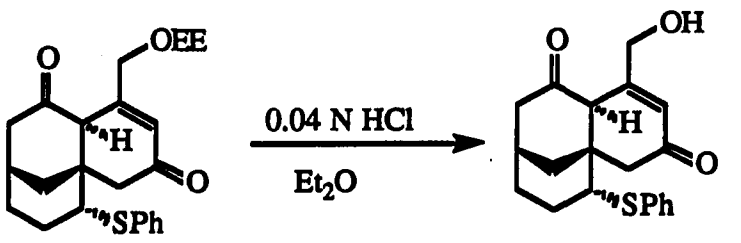
converted to the enone **63** using the Saegusa reaction and then was deprotected with dilute acid in tetrahydrofuran to form the allylic alcohol **66.**











65 66

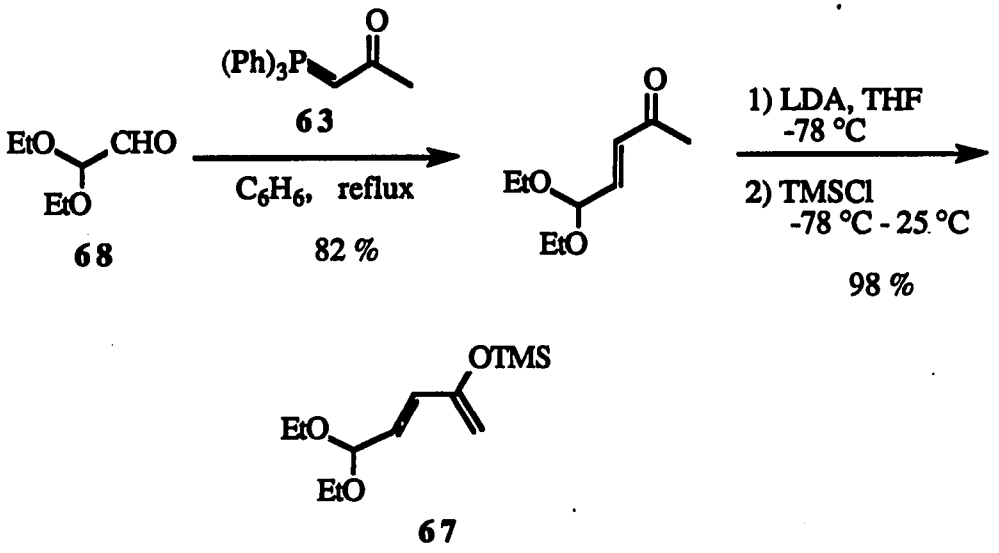
The conversion of the allylic alcohol to the aldehyde proved not to be a simple task. The conditions attempted are reported in Table III. None of the conditions attempted gave

Table III. Oxidation of Allylic Alcohol **66** to Aldehyde **58**

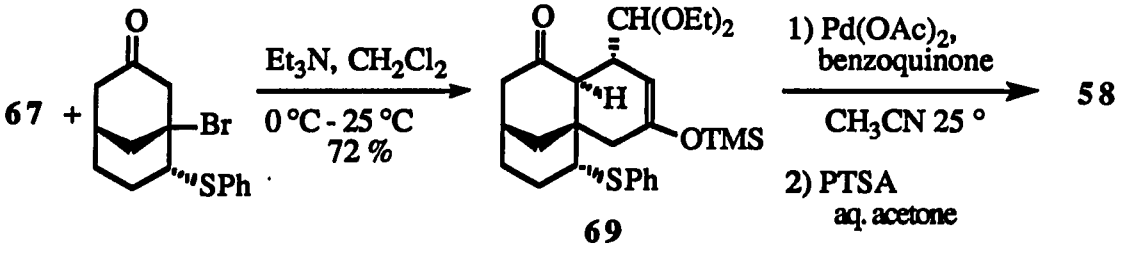
Oxidant	Yield
PDC	53 %
PCC	40 %
Jones	decomposition
$(COCl)_2$, DMSO, Et_3N	no reaction
TFAA, DMSO, Et_3N	no reaction

satisfactory yields of the aldehyde. The best, PDC,[33] produced the aldehyde in 53% yield with significant decomposition of the starting material. Also of note are the attempts with conditions described by Rousch[34] and Franck [35], where in the only detectable product was the starting material.

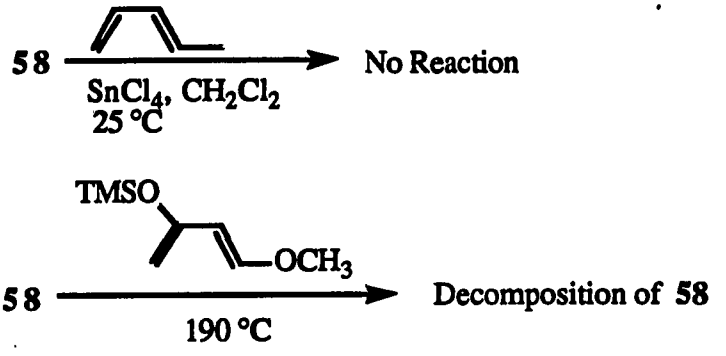
In view of these results, a diene which had the allylic carbon at the proper oxidation state was envisioned. Diene **67** was prepared in a similar manner as diene **60** from the



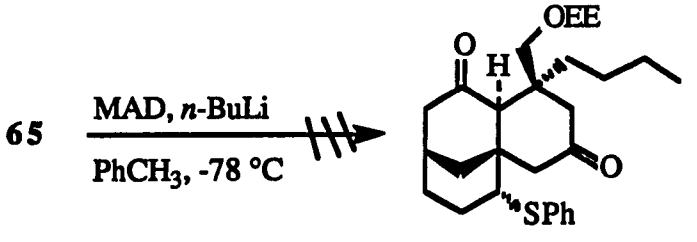
previously reported aldehyde **68**.[36] Diene **67** was used in the bridgehead Diels-Alder reaction to form adduct **69** which was oxidized to the enone using the Saegusa reaction. The acetal was deprotected using PTSA in wet acetone to give the required aldehyde **58**. Two different Diels-Alder reaction conditions were attempted to annulate the fourth



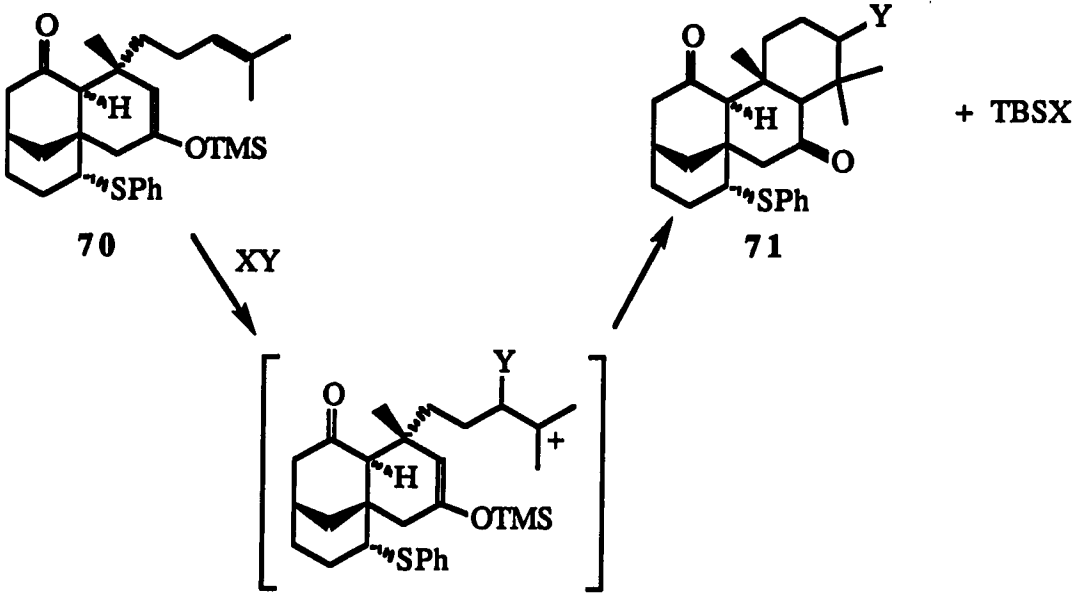
ring of kaurenoid ring system to aldehyde **58**. Using piperylene with Lewis acid catalysis ($SnCl_4$) resulted in the isolation of the starting material. The other attempt with Danishefsky's diene[37] at 190 °C resulted in the decomposition of the aldehyde **58**.



The last avenue in this area that was investigated was a Michael addition to enone **65**. Maruoka and coworkers have reported the 1,4 addtion of organolithiums and Grignard reagents to enones using a excess of methylaluminium bis-(2,6-di-*t*-butyl)-4- methyl-phenoxide (MAD).[38] There has been a report by Stern and Swenton that ketals direct the addition of organolithiums to quinone monoketals using MAD.[39] The ethoxyethyl protecting group in **65** could be used to direct the addition to the enone. This reaction was attempted using *n*-butyl lithium as a model study, but none of the addition product was detected in our system.

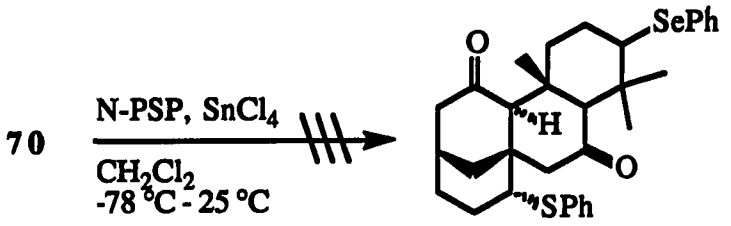


The attention was then turned to the previously reported bridgehead enone Diels-Alder adduct **70**.[17] If this adduct could be cyclized to **71**, all of the carbons of the kaurenoid ring system would be in place. The problem would be reduced to modifing the functionality to produce corymbol. In the key cyclization the trisubstituted double bond has to be activated in the presence of the more electron-rich enol silyl ether. The hope was that the enol silyl ether was sufficiently hindered that a large and soft coordinating group (Y) would preferentially attack the trisubstituted double bond to form **72**. With the knowledge that normal Lewis acids decompose adduct **70**,[40] various reagents were attempted to cyclize adduct **70**.



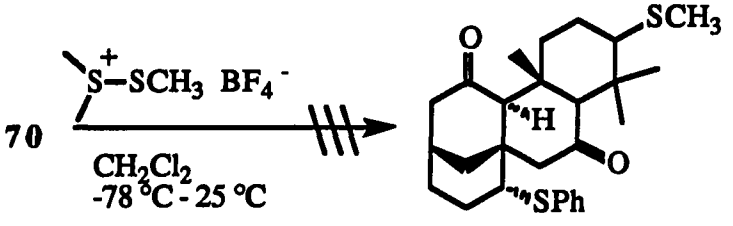
72

The first reagent was N-phenylselenophthalimide (NPSP), previously reported by Nicolaou and coworkers.[41] The reagent has been shown to activate a variety of alkenes to intramolecular nucleophilic attack. In our hands, this reagent did not form the cyclized



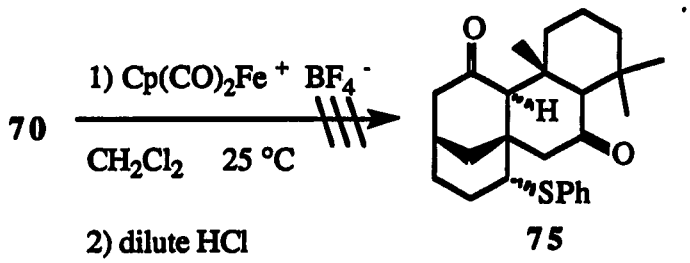
73

product **73**. Another reagent that was attempted was the sterically demanding, weak Lewis acid mercury (II) iodide, but the reaction produced an uncharacterizable product. Next dimethyl-(thiomethyl)sulfonium tetraflouroborate was tried. This reagent, developed by Trost and Murayama,[42] has been shown to activate double bonds to nucleophilic attack, but the same uncharacterizable product was formed as in the mercury (II) iodide case. The reaction was also attempted with a iron complex that has been previously used to activate



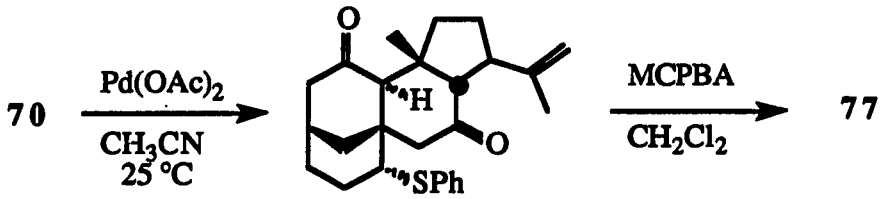
74

double bonds to nucleophilic attack by enol silyl ethers.[43] This reaction condition also did not afford any of the cyclized product **75**.

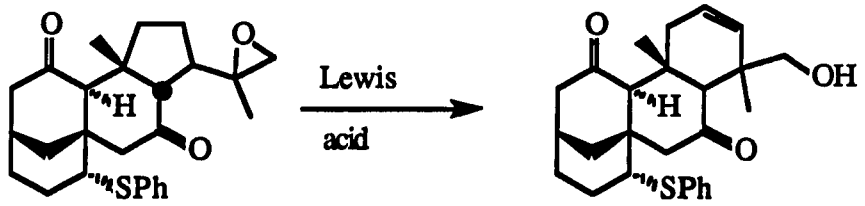


75

Our current strategy is centered around the formation of a five membered ring, then ring expansion to the needed six membered ring. Ito and coworkers have reported the intramolecular cyclization of enol silyl ethers to alkenes.[44] In our system the expected product was **76**. Compound **76** could be oxidized to the epoxide **77** which could be



76



77 78

rearranged to the ring expanded alcohol **78**. Alcohol **78** will allow the synthesis of kaurenoic acids which have important biological activity.

EXPERIMENTAL

General

Unless otherwise stated, reagents used were purchased from commercial suppliers and were not purified unless stated. Dry diethyl ether and tetrahydrofuran were distilled from benzophenoneketyl, benzene was distilled from lithium aluminum hydride, methylene chloride and acetonitrile were distilled from calcium hydride, and toluene was distilled from sodium. Unless otherwise noted, all reactions were conducted in an argon atmosphere. For reactions requiring anhydrous conditions, the apparatus was flamed dried under a stream of argon. Melting points were determined using a Fisher-Johns melting point apparatus and are uncorrected. Silica gel used for flash chromatography was EM Science Kieselgel 60 (230-400 mesh) or Mereck 60 grade (230-400 mesh). Thin layer chromatography was performed using EM Science Kieselgel F_{254} prepared plates with thickness of 0.25 cm. The solvent systems were suitable mixtures of hexanes (H) and ethyl acetate (EA). High field proton nuclear magnetic resonance spectra were obtained at 300 MHz using Nicolet Magnetics Corporation 1280 spectrometer. All chemical shifts are reported in δ relative to tetramethylsilane as an internal standard. Coupling constants (J) are reported in Hz. Splitting patterns are designated: s (singlet), d (doublet), t (triplet), q (quartet), bs (broad singlet), m (multiplet) ABq (AB quartet). Carbon-13 nuclear magnetic resonance spectra were recorded at 75.46 MHz using a Nicolet Magnetics Corporation 1280 spectrometer and are reported in δ relative to the central peak of $CDCl_3$ (77.06 ppm). Infarred spectra were recorded using a Perkin-Elmer 1320 infared spectrophotometer and are reported in cm^{-1}. EI and CI (using the gas reported) low resolution mass spectra were

recorded on a Finnegan 4023 mass spectrometer. High resolution mass spectra were recorded using a Kratos model MS-50 spectrometer.

2,3,4,6,8,9,10,11,12aα-Nonahydro-7α-(phenylthio)-6a,10-methanocyclo[a]napthalene-12,5-dione **46**

To a solution of **48** (632 mg, 1.44 mmol) in 15 mL of CH_3CN at ambient temperature was added $Pd(OAc)_2$ (190 mg, 0.86 mmol) and 1,4-benzoquinone (90 mg, 0.86 mmol). The solution was stirred at ambient temperature for 16 h (a black suspension formed). The suspension was filtered through celite, then concentrated *in vacuo*. The crude product was purified by flash chromatography using 3 : 1 H : EA as elutent to yield 484 mg (92%) of **46**. TLC (3 : 1, H : EA) $R_f = 0.29$. ^1H NMR ($CDCl_3$) δ 1.2-1.5 (m, 3 H), 1.6-1.85 (m, 6 H), 1.9-2.15 (m, 3 H), 2.55-2.15 (m, 6 H), 2.95 (dd, J = 17.2 Hz, 4.9 Hz, 1 H), 3.28 (d, J = 15.9 Hz, 1 H), 3.66 (bs, 1 H), 7.20-7.40 (m, 5 H). ^{13}C NMR ($CDCl_3$) δ 21.59, 22.05, 22.49, 27.93, 28.52, 31.80, 35.25, 43.73, 45.54, 48.69, 57.54, 58.94, 127.40, 129.12, 132.47, 132.86, 134.96, 148.16, 197.83, 211.28. IR ($CDCl_3$ solution) 2935, 2860, 1710, 1662,1620, 1375, 1295, 900, 690 cm^{-1}. Low resolution mass spectrum m/e 55, 67, 84, 109, 215, 257, 366. High resolution mass spectrum for $C_{23}H_{24}BO_2S$ requires 366.16536, measured 366.16599 (+ 1.7 ppm).

7β-Cyano-2,3,4,6,8,9,10,11,12aβ,12bα-decahydro-7α-(phenylthio)-5-[(trimethylsilyl)oxy]-6aα,10α-methanocycloocta[a]napthlene-12-one **53**

To a solution of enone **46** (133 mg, 0.36 mmol) in 3.5 mL of dry toluene at 0 °C, was added freshly distilled cyanotrimethylsilane (0.12 mL, 0.92 mmol). Diethylaluminum chloride (1.8 M in toluene) (0.62 mL, 1.12 mmol) was added dropwise. The solution was

warmed to ambient temperature over 3h, then saturated NH_4Cl (10 mL) was added followed by 5% $NaHCO_3$ (25 mL). The resulting aqueous layer was extracted 3 x 10 mL of benzene, then dried over $MgSO_4$. The crude material was purified by flash chromatography to yield 150 mg (89%) of **53**. TLC (3 : 1 H : EA) $R_f = 0.27$. ^{1}NMR ($CDCl_3$) δ 0.18 (s, 9 H), 1.38 - 2.00 (m, 12 H), 2.10 - 2.65 (m, 8 H), 3.05 (dd, J = 17.2, 4.9 Hz, 1 H), 3.33 (bs, 1 H), 7.15 - 7.28 (m, 3 H), 7.35 - 7.42 (m, 2 H). IR ($CHCl_3$) 3018, 2942, 2860, 2300, 1705, 1660, 1435, 1248, 1110, 850 cm^{-1}. Low resolution mass spectrum m/e 73, 110, 224, 247, 265, 287, 357, 375, 438, 465.

2-(1'-Ethoxyethyl)oxy-acetaldehyde **61**

To 2-butene-1,4-diol **60** (2.0 g, 22.6 mmol) suspended in 40mL of dry methylene chloride at ambient temperature was added ethyl vinyl ether (5.40 mL, 56.5 mmol) and PPTS (0.14 g, 0.57 mmol). The suspension was vigorously stirred (a homogeneous solution resulted after 30 min) for 2 h. The resulting solution was diluted with 50 mL of methylene chloride, and washed 1 x 20 mL water, 2 x 20 mL 5% $NaHCO_3$, and 1 x 20 mL brine. The organic layer was dried over Na_2SO_4. The product was concentrated *in vacuo* to yield 5.05 g (96%) of the diprotected alcohol which was directly used in the ozonolysis. ^{1}H NMR ($CDCl_3$) δ 1.21 (t, J = 7.1 Hz, 6 H), 1.32 (d, J = 5.35 Hz, 6 H), 3.40 - 3.70 (m, 4 H), 4.20 - 4.04 (bq, 4 H), 4.73 (q, J = 5.35 Hz, 2 H), 5.70 (t, J = 3.96 Hz, 2 H). ^{13}C NMR ($CDCl_3$) δ 15.31, 19.80, 60.47, 99.02, 129.04. IR ($CDCl_3$) 2990, 2970, 2950, 1450, 1385, 1130, 1085 cm^{-1}. Low resolution mass spectrum CI (NH_3) m/e 90, 116, 158, 178, 204, 250 (M+ NH_4), 276 (M+ OCH_2CH_2). To the crude product (5.05 g, 1.92 mmol) dissolved in dry methylene chloride (200 mL) at -78 °C was bubbled ozone until a blue color resulted (30 min). The excess ozone was removed by bubbling N_2 into

the solution. Triphenylphosphine (5.53 g, 21.1 mmol) was added in five equal portions at -78 °C over 30 min. The solution was then warmed to ambient temperature, and the solution was concentrated *in vacuo*. The residue was diluted with 75 mL of hexanes and filtered through glass wool to remove the triphenylphosphine oxide. The crude product was distilled at 2 mm Hg in a Kugelrohr oven at 55 °C to yield 4.6 g (72%) of **61**. TLC (3 : 1 H : EA) $R_f = 0.25$. ^{1}H NMR ($CDCl_3$) δ 1.20 (t, J = 7.1 Hz, 3 H), 1.36 (d, J = 5.35 Hz, 3 H), 3.46 - 3.70 (m, 2 H), 4.12 (s, 2 H), 4.81 (q, J = 5.35 Hz, 1 H), 9.73 (s, 1 H). ^{13}C NMR ($CDCl_3$) δ 14.94, 19.24, 61.18, 69.82, 99.69, 200.59. IR (thin film) 2990, 2980, 2720, 1735, 1440, 1380,1340, 721, 695 cm^{-1}. Low resolution mass spectrum CI (NH_3) m/e 90, 132, 150 (M+ NH_4), 176 (M+ OCH_2CH_2), 282 (2M+ NH_4).

5-(1-Ethoxyethyl)oxy-3-penten-2-one **64**

To a solution of **62** (4.0 g, 30.27 mmol) in 75 mL of benzene, was added phospoylide **63** (14.5 g, 45.41 mmol). The resulting suspension was heated at 80 °C for 3.5 h. The solution was cooled to ambient temperature, then concentrated *in vacuo*. The residue was diluted with a 3 : 1 mixture of hexanes : diethyl ether (100ml), then filtered through glass wool. The crude material was purified flash chromatography eluting with 3 : 1 H : EA to yield 3.0g (57%) of **64**. TLC (3 : 1 H : EA) $R_f = 0.36$; ^{1}H NMR ($CDCl_3$) δ 1.20 (t, J = 7.1 Hz, 3 H), 1.35 (d, J = 5.35 Hz, 3 H), 2.29 (s, 3 H) 3.40 - 3.75 (m, 2 H), 4.10-4.35 (m, 2 H), 4.78 (q, J = 5.35 Hz, 1 H), 6.33 (d,J = 15.9 Hz, 1 H), 6.82 (dt, J = 15.9 Hz, 4.5 Hz, 1 H). ^{13}C NMR ($CDCl_3$) δ 15.17, 19.61, 27.67, 60.77, 63.23, 99.29, 129.84, 143.25, 197.99. IR (thin film) 3005, 2990, 2900, 1675, 1635, 1445, 1360,1257 cm^{-1}. Low resolution mass spectrum CI (NH_3) m/e 90, 118, 127, 144, 173 (M+ NH_4), 216 (M+ OCH_2CH_2).

5-[(1'-ethoxyethyl)oxy- 1,3-pentadiene-2-oxy]-trimethylsilane **60**

To a solution of enone **64** (0.86 g, 5.0 mmol) in dry methylene chloride (25 mL) cooled in an ice bath, was added triethylamine (1.39 mL, 10.0 mmol). TMSOTf (1.16 mL, 6.0 mmol) was added dropwise to the stirred solution. The solution was slowly warmed to ambient temperature and stirred for a total of 8 h. The methylene chloride was removed *invacuo*, diluted with 50 mL of hexanes, then decanted. The solution was concentrated *in vacuo* to yield 1.0 g (82%) of **60**. The crude material was of high purity and was not purified before use. ^{1}H NMR ($CDCl_3$) δ 0.23 (s, 9 H), 1.21 (t, J = 7.1 Hz, 3 H), 1.33 (d, J = 5.35 Hz, 3 H), 3.45 - 3.60 (m, 2 H), 4.05 - 4.25 (m, 2 H), 4.31 (s, 2 H), 4.75 (q, J = 5.35 Hz, 1 H), 5.95 - 6.15 (m,J = 15.9 Hz, 2 H), 6.82 (dt, J = 15.9 Hz, 4.5 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 15.17, 19.61, 27.67, 60.77, 63.23, 99.29, 129.84, 143.25, 197.99; IR (thin film) cm^{-1}. Low resolution mass spectrum CI (NH_3) m/e 90, 116, 155, 172, 199, 245 (M+H); High resolution mass spectrum for $C_{12}H_{24}O_3Si$ requires 244.14947, measured 244.1487.

1α-[(1'-Ethoxyethyl)methyloxy]-1,6,7,8,9,10aα-hexahydro-5α-(phenylthio)-3-[(trimethylsilyl)oxy]-4aβ, 8β-methanobenzocycloocten-10-one **59**

To a solution of diene **60** (0.82 g, 3.35 mmol) and bridgehead bromide **28** (0.90 g, 2.79 mmol) in 2.8 mL of dry methylene chloride at 0 °C was added dropwise triethylamine (0.51 g, 3.69 mmol). The resulting solution was slowly warmed to ambient temperature and stirred for 10h. The resulting suspension was diluted with hexanes, then filtered. The crude product could not be separated from **64** by flash chromatography and crude material was taken directly to the next step. An analytical sample was obtained by preparative thin

layer chromatography to yield the following data. TLC (3 : 1, H : EA) R_f = 0.26. ^{1}H NMR ($CDCl_3$) δ 0.19 (s, 9 H), 1.16 (bt, J = 7.0 Hz, 3 H), 1.24 (dd, J = 7.2 Hz, 5.35 Hz, 3 H), 1.30 - 1.68 (m, 3 H), 1.80 - 1.95 (m, 2 H), 2.0 (bs, 1 H), 2.60 - 3.05 (m, 3 H), 3.26 -3.63 (m, 3 H), 4.58 - 4.63 (m, 1 H), 4.95 (d, J = 5.2 Hz2 H), 4.75 (q, J = 5.35 Hz, 1 H), 7.18 - 7.32 (m, 3 H), 7.38 - 7.43 (m, 2 H). ^{13}C NMR δ .14, 29.55, 34.81, 38.74, 40.23, 41.80, 46.17, 50.49, 60.60, 66.46, 68.95, 89.07, 98.26, 99.79, 103.25, 126.96, 128.91, 132.42, 133.33, 135.52, 149.86, 150.38, 214.02. IR (thin film) 2980, 2940, 1690, 1480, 1250, 1180, 1090, 900, 850 cm^{-1}. Low resolution mass spectrum m/e 73, 110, 153, 247, 291, 385, 398, 488.

1-[(1'-Ethoxyethyl)methyloxy]-6,7,8,9,10aα-pentahydro-5α-(phenylthio)-4aβ, 8β-methanobenzocycloocten-3,10-dione **65**

To a solution of crude **59** (0.90 g) in 25 mL of dry acetonitrile at ambient temperature was added $Pd(OAc)_2$ (310 mg, 1.40 mmol) and 1,4-benzoquinone (150 mg, 1.40 mmol) . The mixture was stirred for 10 h at ambient temperature. The resulting black suspension was purified by flash chromatography and yielded 0.72 g (62%) of **65**. TLC (3 : 1 H : EA) R_f = 0.31; ^{1}H NMR δ 1.10 - 1.40 (m, 2 H), 1.45 - 1.60 (m, 2H), 1.95 - 2.10 (m, 2 H), 2.25 - 2.60 (m, 3 H), 2.98 (dd, J = 14 Hz, 6 Hz, 1 H), 3.30 (d, J = 16.5 Hz, 1 H), 3.42 - 3.65 (m, 1 H), 3.70 - 4.20 (m, 2 H), 4.62 - 4.75 (m, 1 H), 6.32 (d, J = 8.3 Hz, 1 H), 7.21 - 7.32 (m, 3 H), 7.36 - 7.45 (m, 2 H). ^{13}C NMR δ 28.22, 30.28, 31.80, 38.63, 39.34, 44.94, 53.91, 54.94, 58.89, 60.98, 61.19, 64.13, 99.46, 125.50, 127.61, 129.22, 152.62, 134.66, 137.09, 140.90, 197.98, 214.02. IR ($CDCl_3$) 2980, 2925, 1705, 1675, 1630, 1480, 1380, 1230, 1135, 1085, 900, 685.

1-(hydroxymethyl)-6,7,8,9,10aα-pentohydro-5α-(phenylthio)-

4aβ, 8β-methanobenzocycloocten-3,10-dione **66**

To a solution of enone **65** (0.72 g, 1.74 mmol) in 200 mL of THF at ambient temperature, was added 0.04 N HCl (60 mL). The solution was stirred for 12 h at ambient temperature. The crude material was purified by flash chromatography eluting with 3 : 1 H : EA to yield 0.40 g (67%) of **66**. TLC (3 : 1 H : EA) $R_f = 0.24$. ^{1}H NMR δ 1.38 - 1.40 (m, 4 H), 1.80 - 2.14 (m, 2 H), 2.22 - 2.42 (m, 4 H), 2.46 (bs, 1 H), 3.00 (dd, J = 14 Hz, 6 Hz, 1 H), 3.31 (d, J = 15.5 Hz, 1 H), 3.91 (bs, 1 H), 4.02 (dd, J = 16.5 Hz, 6 Hz, 1 H), 6.32 (bs, 1 H), 7.24 - 7.35 (m, 3 H), 7.38 - 7.48 (m, 2 H). IR ($CDCl_3$ solution) 3420, 2950, 2900, 1680, 1645, 1445, 1360,1257, 1050 cm^{-1}.

REFERENCES

1. Warner, P. M. *Chem. Rev.* **1989**, *89*, 1067.
2. Kraus, G. A.; Hon, Y.-S.; Thomas, P. J.; Laramay, S.; Liras, S.; Hanson, J. *Chem. Rev.* **1989** *89*, 1591.
3. House, H. O.; Kleschick, W. A.; Zaiko, E.J. *J. Org. Chem.* **1978**, *43*, 3653.
4. House, H. O.; Lee, T. V. *J. Org. Chem.* **1979**, *44*, 2819.
5. House, H. O. DeTar, M. B.; VanDerveer, D. *J. Org. Chem.* **1979**, *44*, 3793.
6. House, H. O.; DeTar, M. B.; Sieloff, R. F.; VanDerveer, D. *J. Org. Chem.* **1980**, *45*, 3545.
7. House, H. O.; Haack, J. L.; McDaniel, W. C.; VanDerveer, D. *J. Org. Chem.* **1978**, *48*, 1643.
8. House, H. O.; Outcult, R. J.;Haack, J. L.; VanDerveer, D. *J. Org. Chem.* **1980**, *45*, 3545.
9. Campbell, K. A.; House, H. O.; Surbur, B. A.; Trahanovsky, W. S. *J. Org. Chem.* **1987**, *52*, 2474.
10. Bestmann, H. J.; Schade, G. *Tetrahedron Lett.* **1982**, *23*, 3543.
11. Magnus, P.; Gallagher, T.; Brown, P.; Huttman, J. C. *J. Am. Chem. Soc.* **1984**, *106*, 2106.
12. Kraus, G. A.; Hon, Y. -S. *Heterocycles* **1987**, *25*, 377.
13. Heathcock, C. H.; Kleinman, E. F.; Binkley, E. S. *J. Am. Chem. Soc.* **1982**, *104*, 1054.
14. Kraus, G. A.; Yi, P. *Synth. Commun.* **1988**, *18*, 473.

15. Kraus, G. A.; Thomas, P. J.; Hon, Y. -S. *J. Chem. Soc., Chem. Commun.* **1987**, 1849.

16. Kraus, G. A.; Hon, Y. -S. *J. Org. Chem.* **1986**, *51*, 116.

17. Kraus, G. A.; Hon, Y. -S.; Sy, J.; Raggon, J. *J. Org. Chem.* **1988**, *53*, 1397.

18. Hoffman, R.; Woodward, R. B. *J. Am. Chem. Soc.* **1965**, *87*, 4388.

19. Kraus, G. A.; Liras, S. *Tetrahedron Lett.* **1989**, *30*, 1907.

20. Liras, S. Ph.D. Thesis, Iowa State University, 1989.

21. Perezamador, M. C.; Jimenez, F. G. *Tetrahedron* **1966**, 1937.

22. Kraus, G. A.; Hon, Y. -S.; Sy, J. *J. Org. Chem.* **1986**, *51*, 2625.

23. Quin, L. D.; Symmes, C., Jr. *J. Org. Chem.* **1976**, *41*, 238.

24. Ito, Y.; Hiro, T.; Saegusa, T. *J. Org. Chem.* **1978**, *43*, 1011.

25. Lipshutz, B. H.; Wilhelm, R. S.; Kozlowski, J. A. *J. Org. Chem.* **1984**, *49*, 3938.

26. Yamamoto, Y.; Yamamoto, S.; Yatagi, H.; Isihara, Y.; Maruyama, K. *J. Org. Chem.* **1982**, *47*, 119.

27. a) Corey, E. J.; Boaz, N. W. *Tetrahedron Lett.* **1985**, *26*, 6015. b) Corey, E. J.; Boaz, N. W. *Tetrahedron Lett.* **1985**, *26*, 6019.

28. Utimoto, K.; Obayashi, M.; Shishiyama, Y.; Innoue, M.; Nozakki, H. E. *Tetrahedron Lett.* **1980**, *21*, 3389.

29. Marshall, J. A.; Anderson, N. H.; Schlicher, J. W. *J. Org. Chem.* **1970**, *35*, 858.

30. Payne, G. B. *Tetrahedron* **1962**, *18*, 763.

31. Minami, I.; Takkahashi, K.; Shimizu, I.; Kimura, T.; Tsuji, J. *Tetrahedron* **1986**, *42*, 2971.

32. Ramirez, F.; Dershowitz, S. *J. Org. Chem.* **1957**, *22*, 41.

33. Corey, E. J.; Schimdt, G. *Tetrahedron Lett.* **1979**, *20*, 399.

34. Roush, W. R. *J. Am. Chem. Soc.* **1980**, *102*, 1390.

35. Franck, R. W.; John, J. V. *J. Org. Chem.* **1980**, *45*, 1170.

36. Bestmann, H. J.; Ermann, P. *Chem. Ber.* **1983**, *116*, 3264.

37. Danishefsky, S.; Yan, C. F.; Singh, R. K.; Gammill, R. B.; McMurry, P. M., Jr.; Fritsch, N.; Clardy, J. *J. Am. Chem. Soc.* **1979**, *101*, 7001.

38. Maruoka, K.; Nonoshita, K.; Yamamoto, S. *Tetraheron Lett.* **1987**, *28*, 5723.

39. Stern, A. J.; Sweton, J. S. *J. Chem. Soc., Chem. Commun.* **1988**, 1255.

40. Sy, J. Department of Chemistry, Iowa State University, personal communication, 1989.

41. Nicolaou, K. C.; Claremon, D. A.; Barnette, N. E.; Seitz, S. P. *J. Am. Chem. Soc.* **1979**, *101*, 3704.

42. Trost, B. M.; Murayama, E. *J. Am. Chem. Soc.* **1981**, *103*, 6529.

43. Rosan, A.; Rosenblum, *J. Org. Chem.* **1975**, *40*, 3621.

44. Ito, Y.; Aoyama, H.; Hairao, T.; Mochizuki, A.; Saegusa, J. *J. Am. Chem. Soc.* **1980**, *102*, 4519.

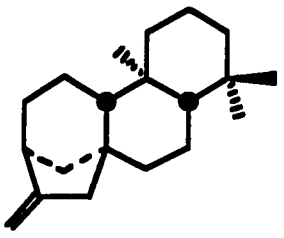
PART II: AN ATTEMPTED CONVERGENT APPROACH TO KAURENE NATURAL PRODUCTS

INTRODUCTION

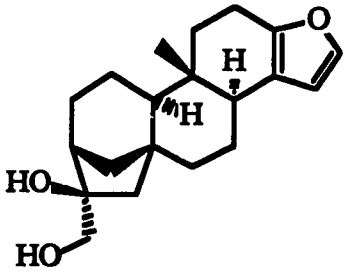
This manuscript will describe an attempted convergent approach to kaurene natural products. The first approach was planned to use a Michael addition followed by an oxy-ene reaction to construct an advanced intermediate. The precursor to the oxy-ene reaction could not be prepared, so other types of cyclization were attempted. These approaches were also unsuccessful. A planned approach is also presented, but this approach has not been tested at this time.

HISTORICAL

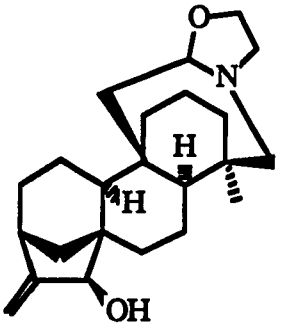
Kaurenes are a subclass of the family tetracyclic diterpene natural products.[1] Examples of this class of natural products are kaurene **1**,[2] the furandiol cafestol **2**,[3] the diterpene alkoloid garryfoline **3**,[4] 7-hydroxykaurenolide **4**,[5] and our synthetic target



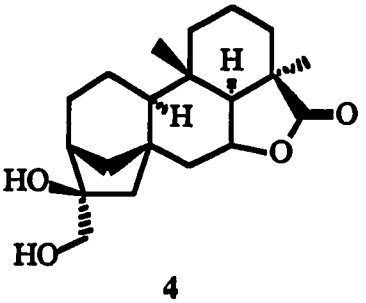
1



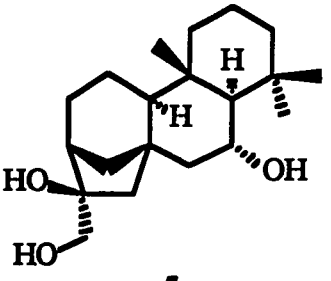
2



3



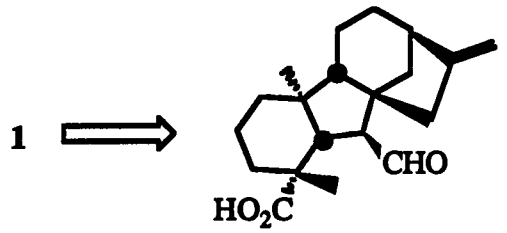
4



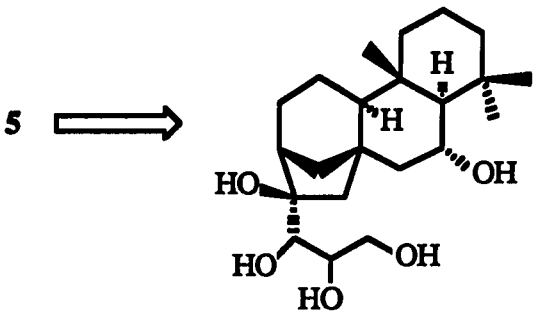
5

corymbol **5**.[6] Of interest is that the higher functionalized members of this class are derived from (-) kaurene not (+) kaurene. The biological activity of this class is varied. Both kaurene **1** and corymbol **5** have been proposed as intermediates in the biosynthesis of natural products. (+) Kaurene has been proposed as a key intermediate in a variety of

gibberlen plant growth regulators, such as **6**.[7] Perezamador and Jiminez[6] have proposed corymbol as the precursor of turbicoryn **7** which was isolated in 1964.[8]

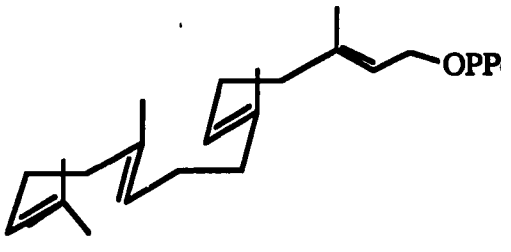


6

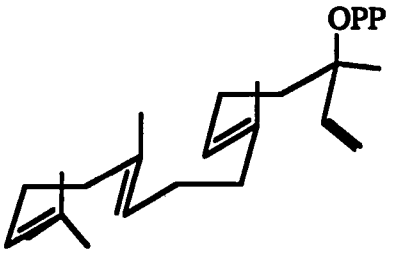


7

All diterpene natural products have geranyl geraniol pyrophosphate **8** or geranyl linalool pyrophosphate **9** as a common ancestor in their biosynthetic pathway,.[1] The



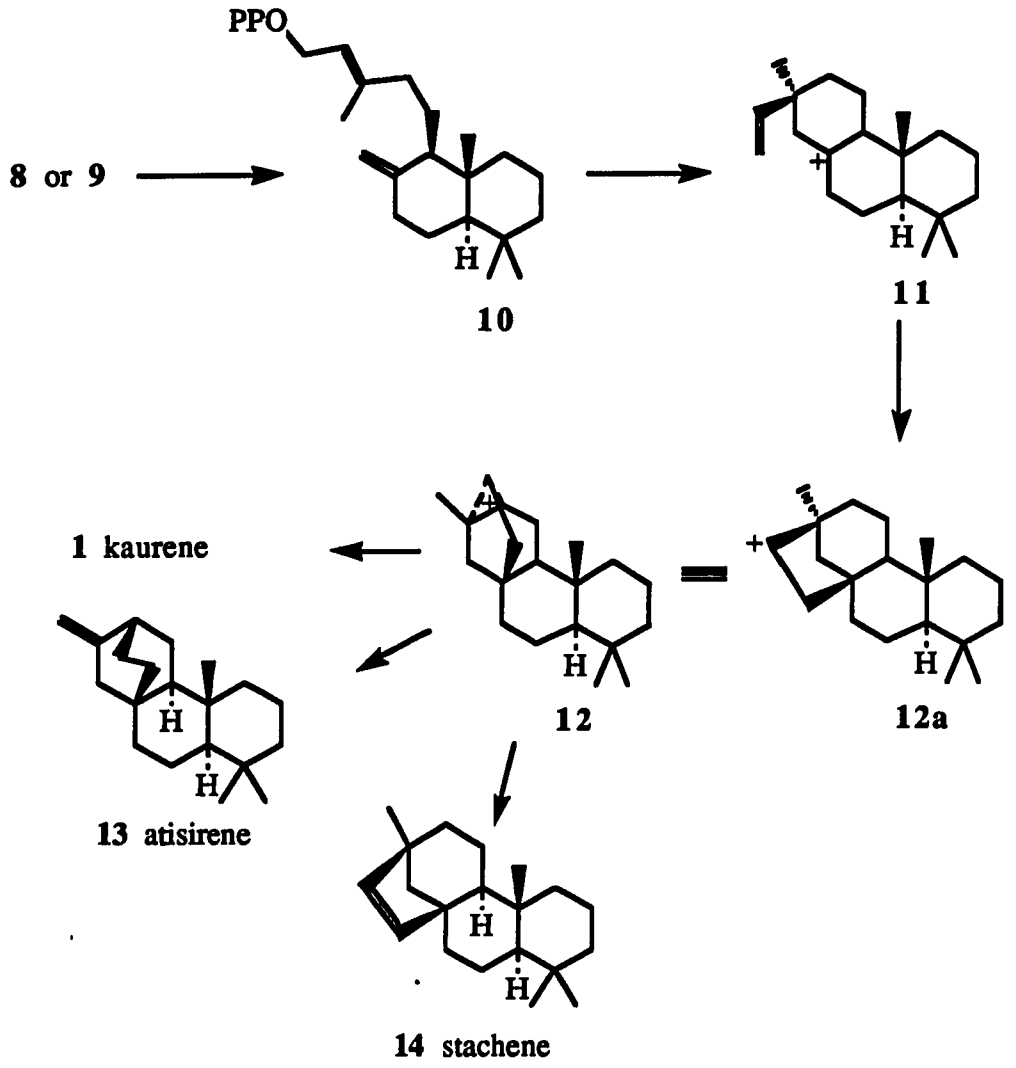
8



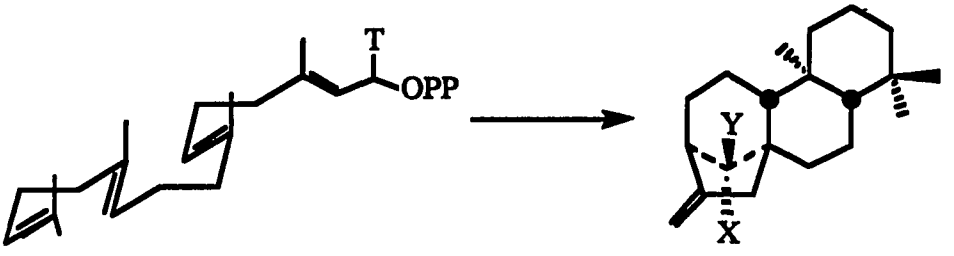
9

accepted biosynthetic pathway of tetracyclic, diterpene natural products was proposed by Wenkert in 1955 (Scheme I).[9] The first step was the formation of copalyl pyrophosphate

Scheme I



10,[10] which was later proved by Sheeter and West[11a] and Fall and West.[11b] The second step was the formation of carbocation **11** by a carbocation cyclization, it is trapped by the vinyl group to provide the nonclassical carbocation **12**. The mode of carbocation collapse determined whether kaurene **1**, atisirene **13**, or stachene **14** natural products are produced. Kaurene is a product of a Wagner-Meerwein shift of intermediate **12a**. In 1980 Coates and Cavender reported their investigation into the stereochemistry of the conversion of copalyl pyrophosphate **10** to kaurene **1**.[12] They synthesized geranyl geraniol pyrophosphate-1-tritium **15** as a racemic mixture (**15a**) and the pure S form (**15b**). These products were separetly converted to (-) kaurene-14-t (**16**) using enzyme preparations from *Marah macrocarpus*. These products were transformed to ketone **17** in five steps. The ring

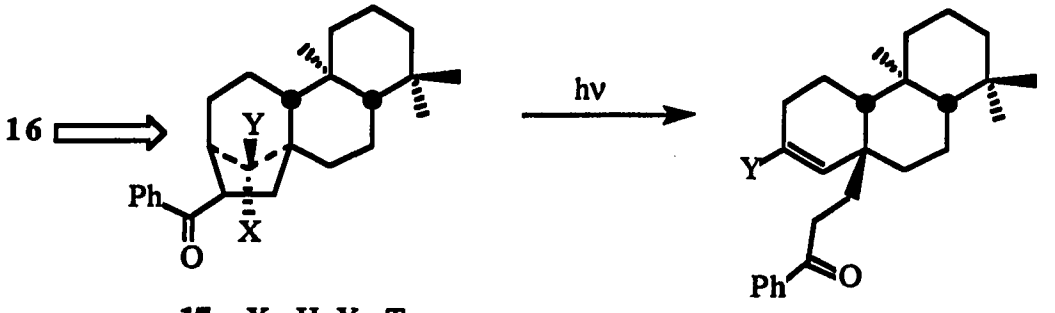


15 a C_1 R,S

15 b C_1 S

16a X =T, Y =H

16b X = T, Y = H



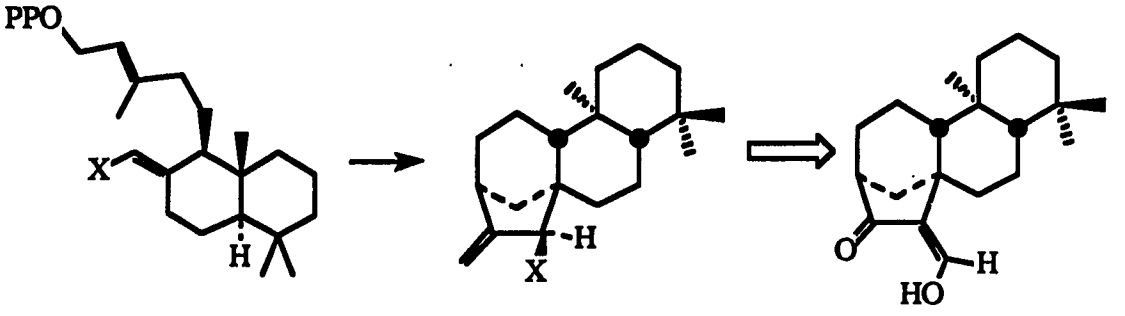
17a X =H, Y =T

17b X = T, Y = H

18a X =H, Y =T

18b X = T, Y = H

opened product **18** was then provided by a photolysis of ketone **17**. In the case of **15a** 59% of the tritium had been retained, whereas 99% of the tritium had been lost in **15b**. From this result Coates and Cavender infers that the product from **15b** is **16b** which was the product of a net inversion at C -1 of **15b**. They also synthesized copalyl pyrophosphate- 17(E)-tritium (**19a**) or S 17(E)-deuterium (**19b**). In this study **19** was converted to (-) kaurene-15- tritium (**20a**) and 15-deuterium (**20b**) using the same enzyme.



19a X = T
19b Y = D

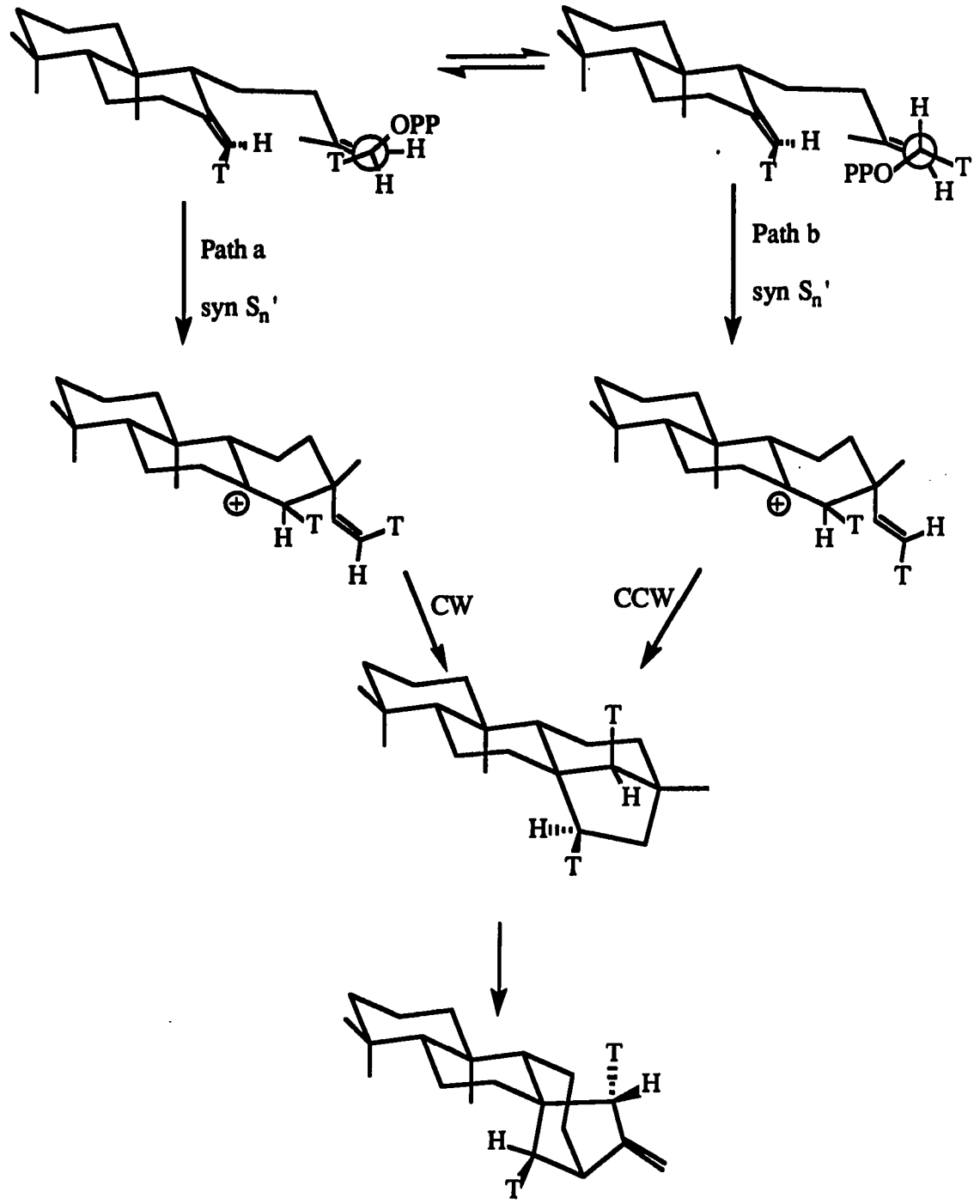
20a X = T
20b X = D

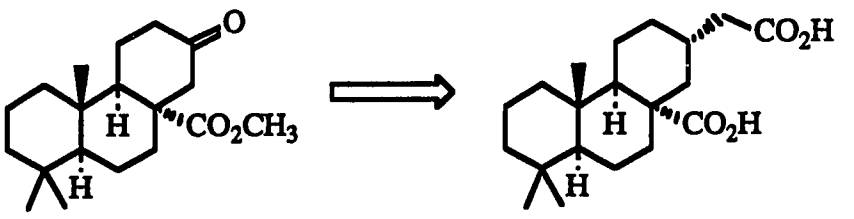
21

They determined using equilibrium deuterium exchange reactions that the tritium and deuterium was contained at the exo position. This was further verified by the conversion of **20a** to **21**, since essentially all of the tritium had been lost. From the data, Coates proposed two possible mechanisms (Scheme II). Coates and Cavender contend that the anti S_N' pathway (path a) is favored over the syn S_N' pathway (path b) by the prinicple of least motion.

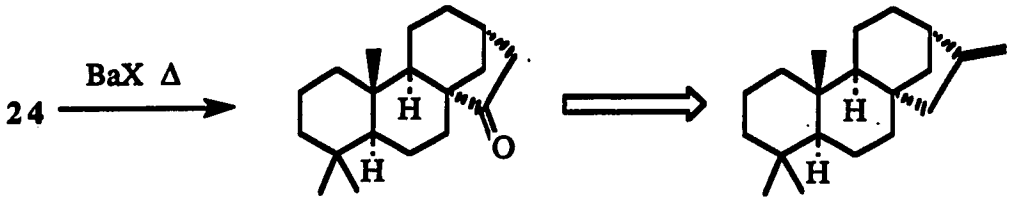
The bicyclic ring system of diterpene natural products have been synthesized by a variety of methods. One of the first reports was the synthesis of the kaurene diterpene phyllocladine **22** by Turner and Ganshirt in 1961.[13] They converted the keto ester **23**[14]

Scheme II


OPP
H
T
H
T
H
H
T
PPO
T
H
Path a
syn S_n'
Path b
syn S_n'
H
T
T
H
H
T
H
T
CW
CCW
T
H
H
T
T
H
H
T



23 24

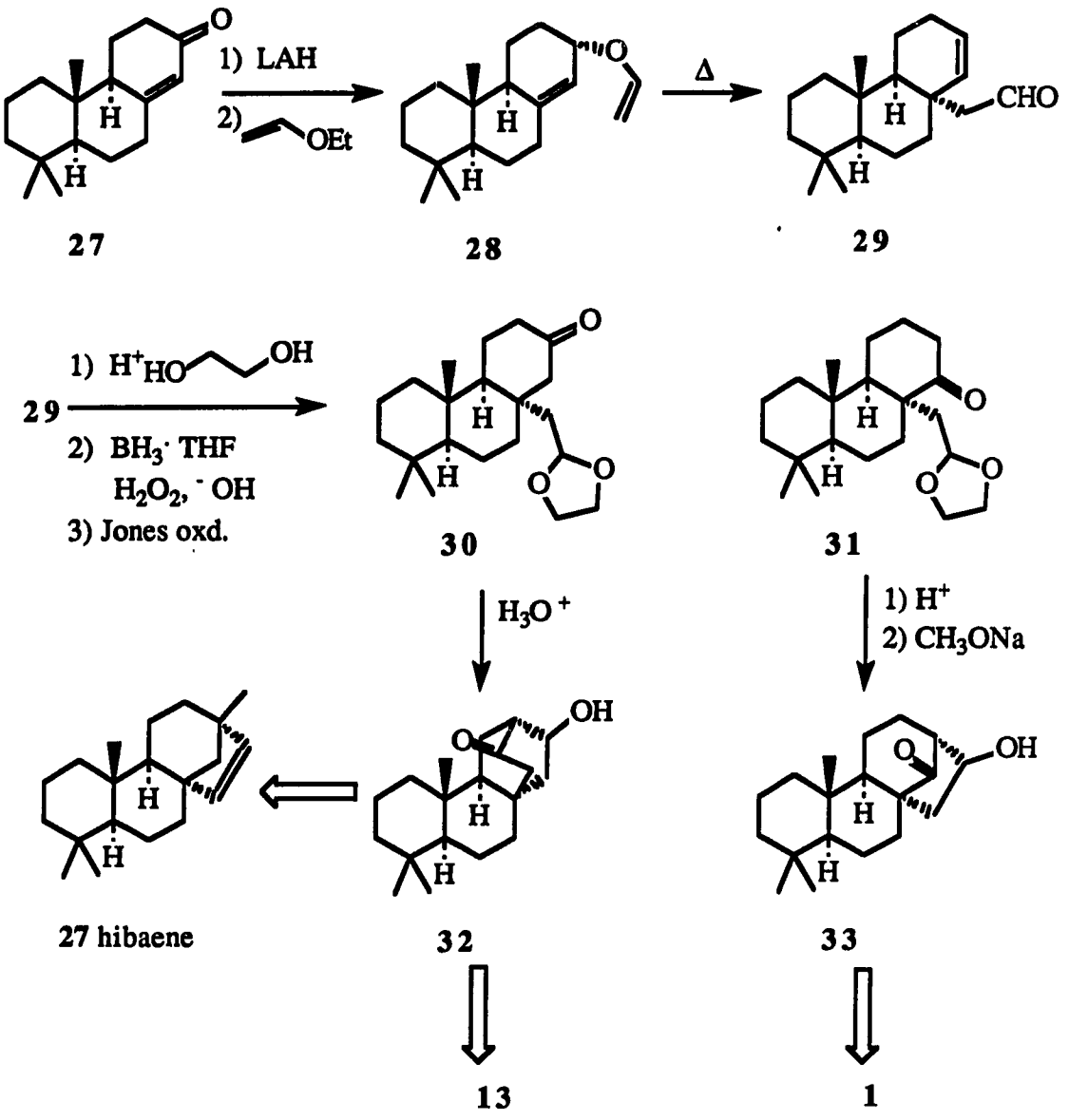


25 22

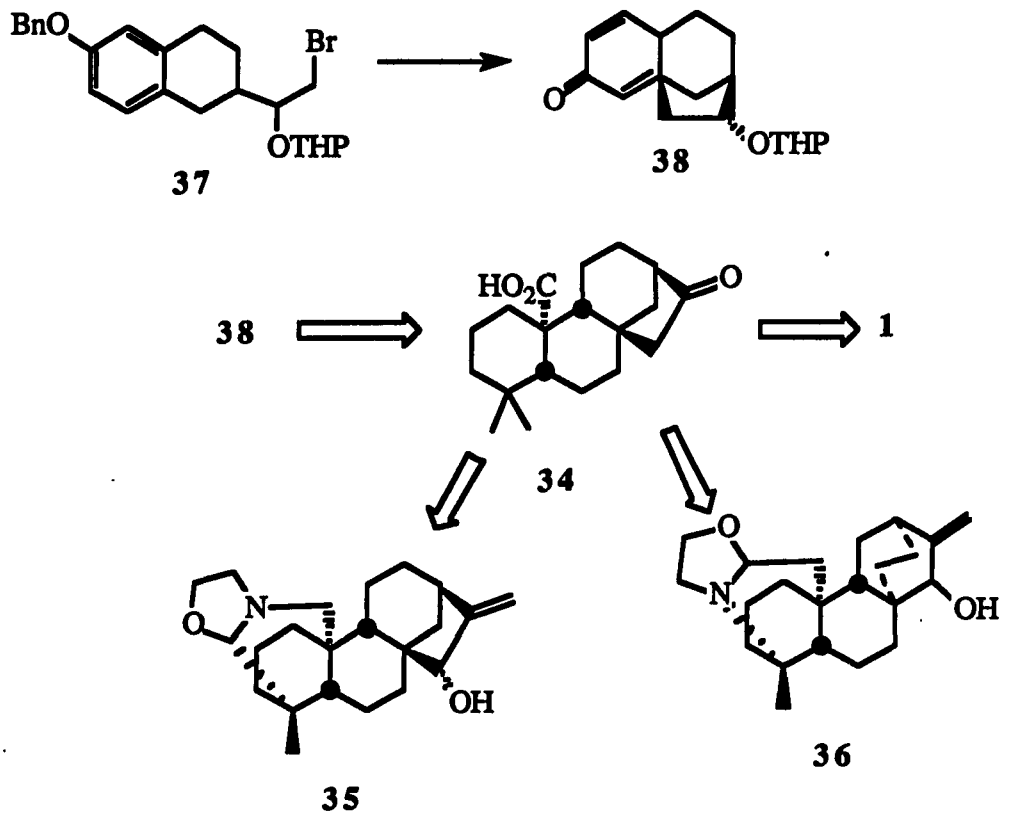
to the diacid **24**. The barium salt of **24** was heated to provide ketone **25**. Ketone **25** was then converted to phyllocladene.

Bell and Ireland developed a versatile method that allowed for the synthesis of kaurene **1**,[15] atisirene **13**,[16] and hibaene **26**.[16] Their strategy was based on a Claisen rearrangement to construct a unit for the bicyclic ring system. Enone **27**[17] was reduced and the resulting alcohol was converted to enol ether **28**. The aldehyde was protected as an ethylene acetal, and the alcohol was oxidized to a mixture of ketones **30** and **31**. Ketone **30** was converted to aldol product **32** which was used as a precursor to atisirene **13**. After deprotection of ketone **31**, aldol product **33** was provided upon treatment with sodium methoxide. This intermediate was converted to kaurene **1**. Ketone **31** was also used in the synthesis of a stachene diterpene, hibaene **26**

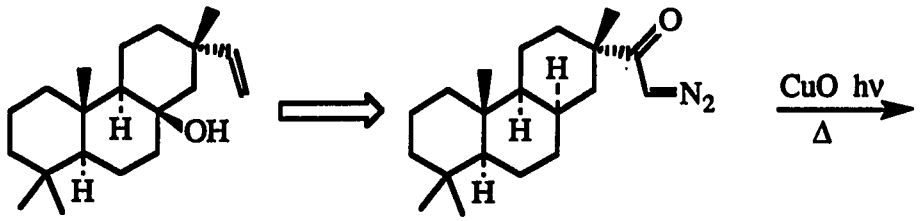
Masamune has developed a synthesis of keto acid **34**[18] which was used as a common intermediate in the synthesis of kaurene **1**,[19] garryime **35**,[20] and atisine **36**.[21]

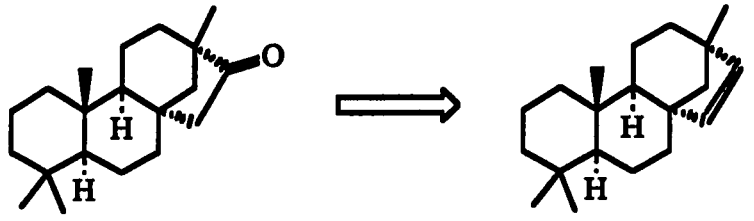


Keto acid **34** was synthesized from phenol **37** . The key in Masamune's synthesis is the intramolecular alkylation to form the tricyclic dienone **38.** This was accomplished by treating **37** with potasium *t*-butoxide. Dienone **38** was converted to acid **34** using standard functional group manipulations.



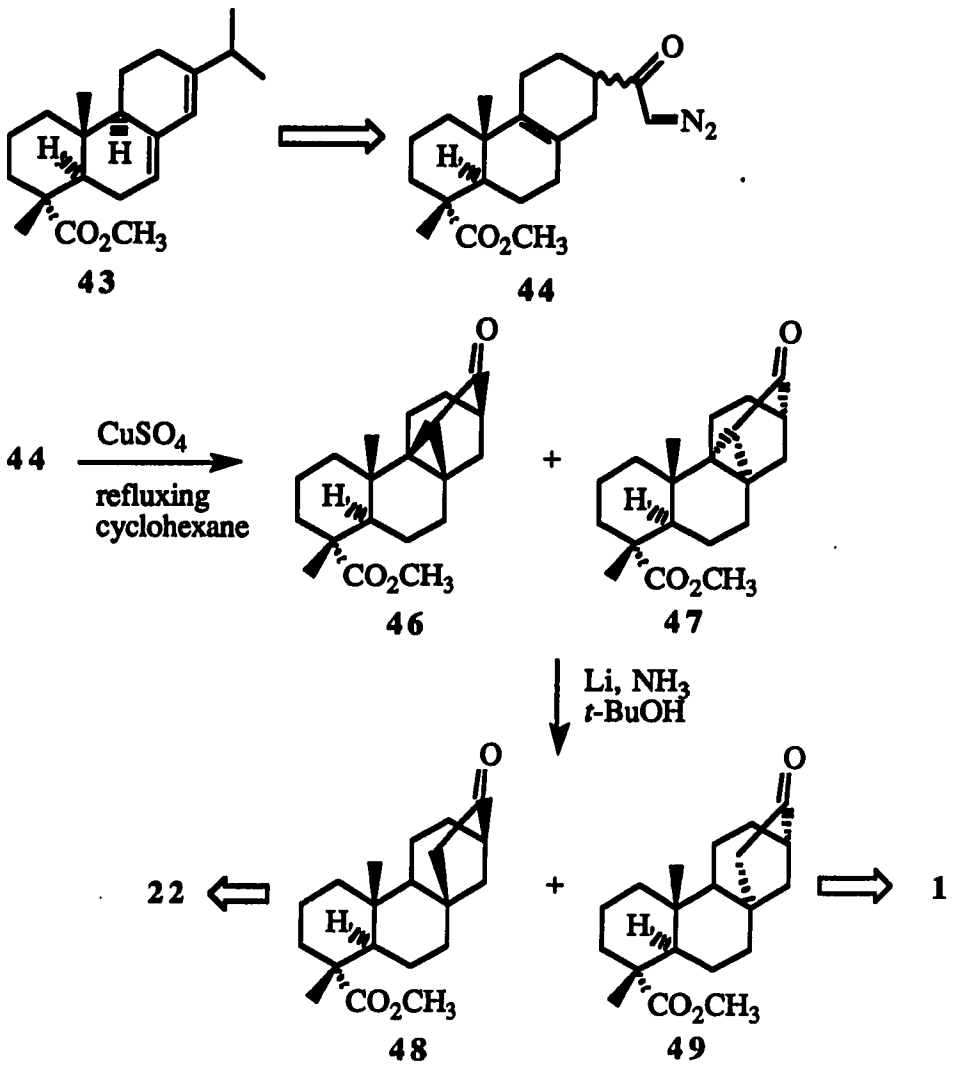
Carbenes have been useful intermediates in the construction of the bicyclic unit of tetracyclic diterpenes. In a synthesis of isohibaene **39** by Kitadani and coworkers the bicyclic ring system was constructed by a carbene insertion into a carbon - hydrogen bond.[22] Enol **40** was transformed to the β– diazoketone **41**. Upon heating **41** in cyclohexane in the presence of copper (II) oxide and light, the tetracyclic ketone **44** was provided. Ketone **42** was then used to prepare isohibaene **39**. Tahara and coworkers used a similar strategy in their synthesis of phyllocladene **22** and kaurene **1**.[23] Starting with abietic acid **43** (available from pine resin), diazoketone **44** was synthesized. Heating ketone **45** in the presence of copper (II) sulfate formed the carbene which added across the double bond to provide a 1 : 1 mixture of cyclopropanes **46** and **47**. These cyclopropanes

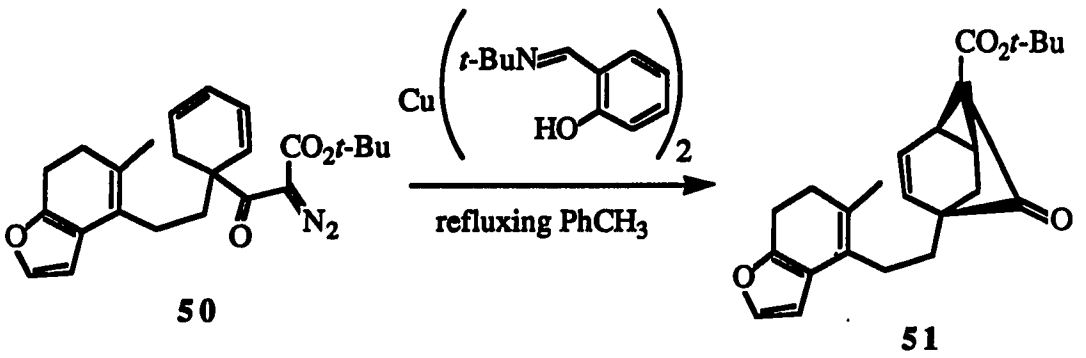




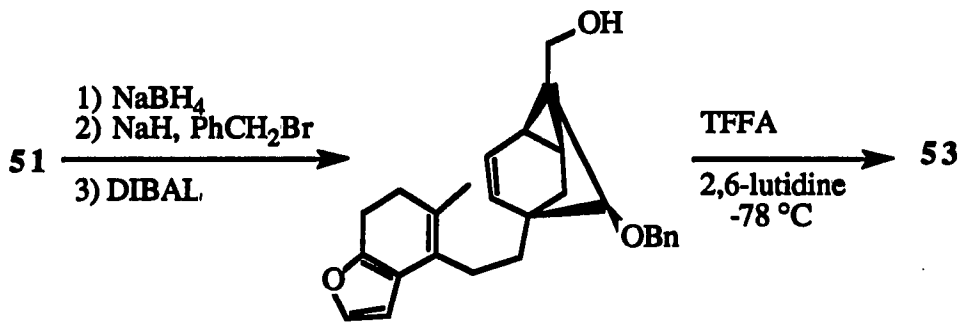
were reduced with lithium in liquid ammonia to form tetracyclic ketones **48** and **49**. Ketone **48** was used in the synthesis of phyllocladene **22**. Ketone **49** was used in the synthesis of kaurene **1**.

In a report of the total synthesis of cafestol **2**, Corey and coworkers used a carbene insertion into a double bond to prepare a precursor of corymbol. [24] Diazoketone **50** was decomposed to the carbene by heating **50** with copper (II) bis-(salicylaldehyde-*t*-butyl-amine) to provide keto ester **51**. The keto ester was converted to alcohol **52** in three steps. Alcohol **52** was then employed in an acid catalyzed cyclization to synthesized pentacycle **53**. Pentacycle **53** was then converted to corymbol **2**.

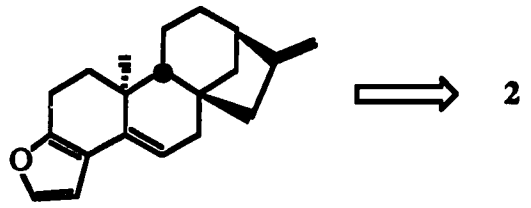

H
H
CO2CH3
43
O
N2
CO2CH3
44
44
CuSO4
refluxing
cyclohexane
O
CO2CH3
46
+
O
CO2CH3
47
Li, NH3
t-BuOH
22
O
CO2CH3
48
+
O
CO2CH3
49
1


CO2t-Bu
t-BuN
Cu
HO
2
N2
O
refluxing PhCH3
CO2t-Bu
O

50 51


1) NaBH4
2) NaH, PhCH2Br
3) DIBAL
51
OH
OBn
TFFA
2,6-lutidine
-78 °C
53

52

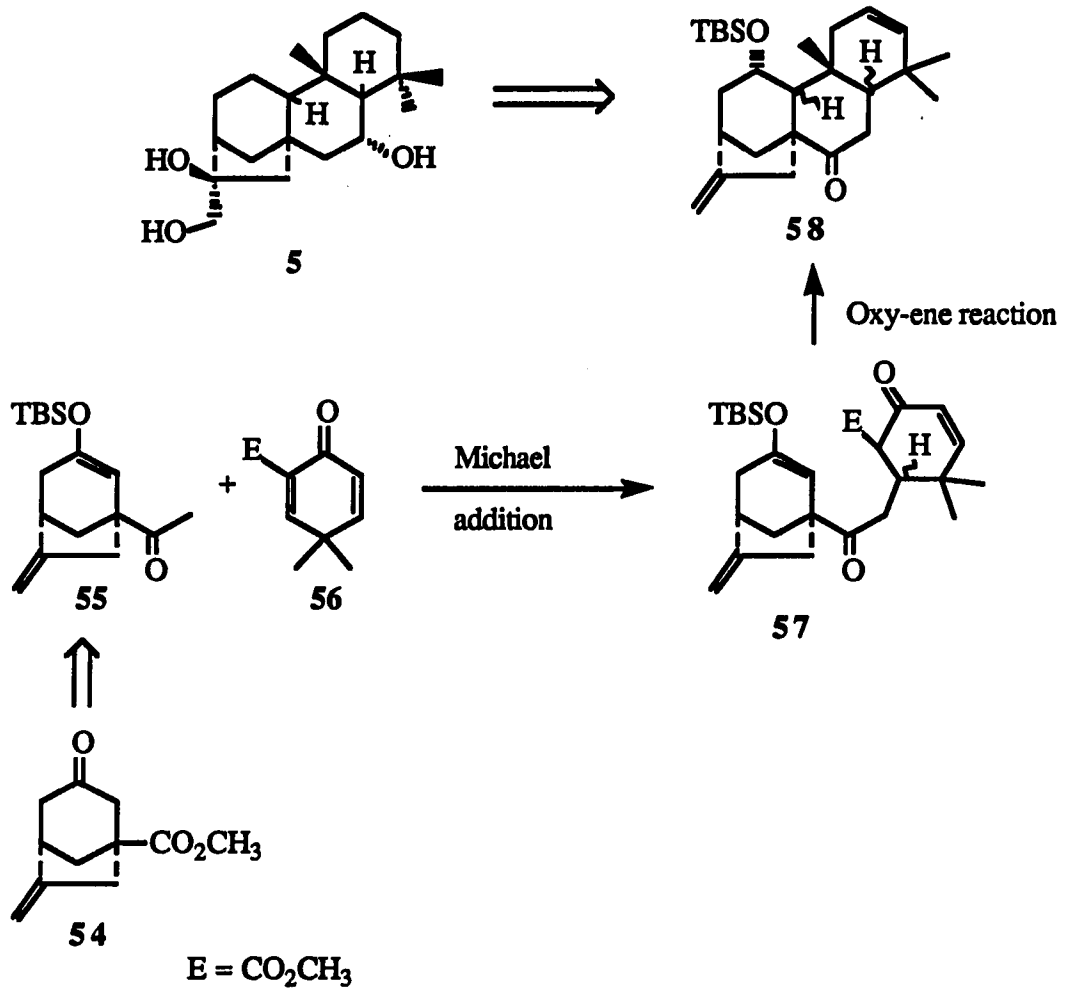

2

53

RESULTS AND DISCUSSION

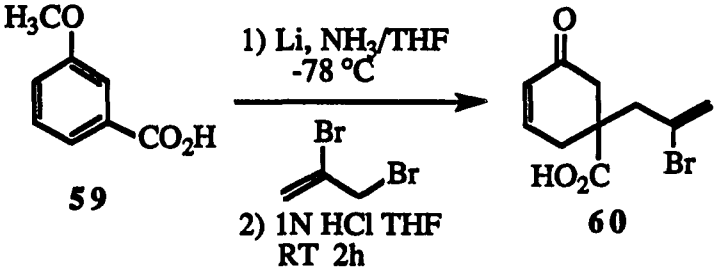
The bicyclo [3.2.1] octene **54** previously reported by Marinovic and Ramanathan[25] appeared to be an attractive starting point for a convergent route to kaurene natural products. This route would entail a Michael addition followed by an oxy-ene reaction to construct the tetracylic ring system (Scheme I). The elegance of this approach

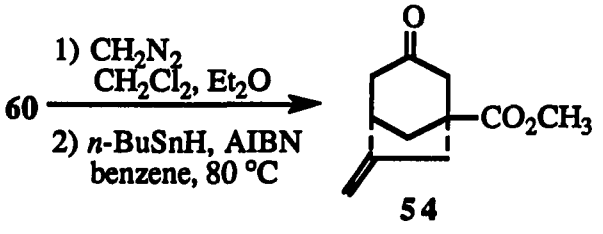
Scheme I



would be the few steps required to construct a tetracyclic ring system which contains varied functionality that would allow the synthesis of many members of this class. This route would require the transformation of **54** to the Michael donor **55**. Ketone **55** will be used in a Michael addition with the readily available dienone **56** to give the tricyclic oxy-ene precursor **57**, which would be employed in the oxy-ene reaction to afford the key tetracyclic intermediate **58**.

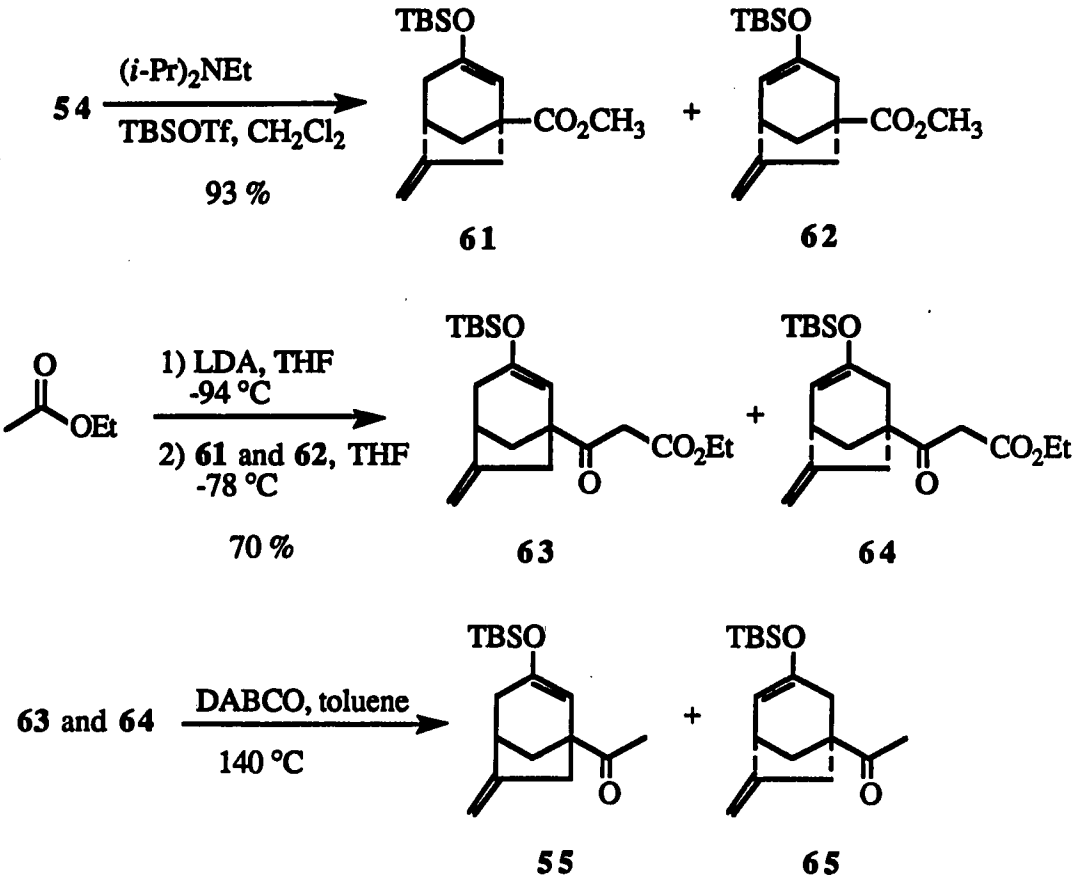
The bicyclic keto-ester **54** was synthesized in a three step sequence[25] starting with *m*-anisic acid **59**. *m*-Anisic acid was reductively alkylated with 2,3-dibromopropene





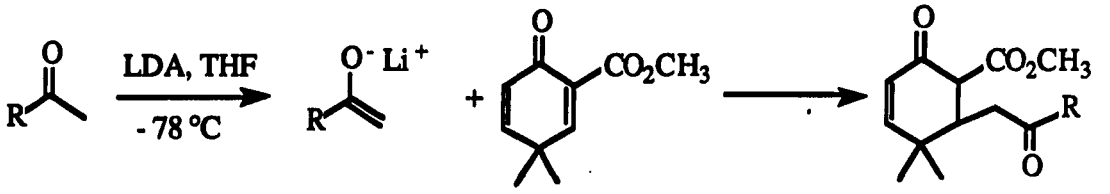
followed by acidic workup to yield the enone **60** in 67% yield. The acid-enone **60** was esterified with diazomethane, then the [3.2.1] bicyclic ring system was formed via a vinylic radical cyclization (*n*-Bu_3SnH, AIBN) to yield the bicyclic keto ester **54** in 59 % yield. The ester **1** was then transformed to the required enol ether **55** in three steps. The mixture of enol silyl ethers **62** and **63** were formed by reacting the keto-ester **54** with

N,N-diisopropylethlyamine and *t*-butyldimethylsilyl triflate (TBSOTf).[26] The mixture of **61** and **62** was condensed with the lithium enolate of ethyl acetate to give the mixture of β–keto-esters **63** and **64** which were decarboalkoxylated with diazabicyclo [2.2.2] octane (DABCO)[27] to form a mixture of **55** and **65**.



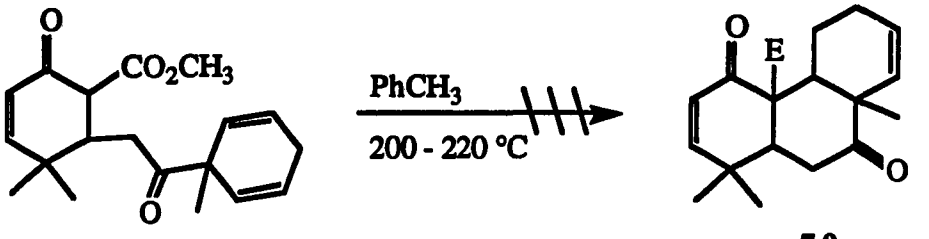
The feasibility of the Michael addition and the oxy-ene reaction sequence was tested with model studies. The results of the Michael additions to the known dienone **56**[28] are contained in Table 1. The Michael adducts were formed in fair to good yields as

Table 1. Michael Additions to Ester Dienone **56**

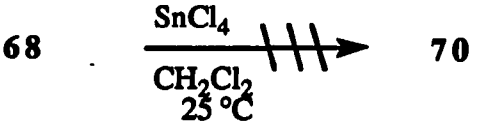


Methyl Ketone	Adduct	R	% yield
	66		83
	67		45
	68		50
	69		33

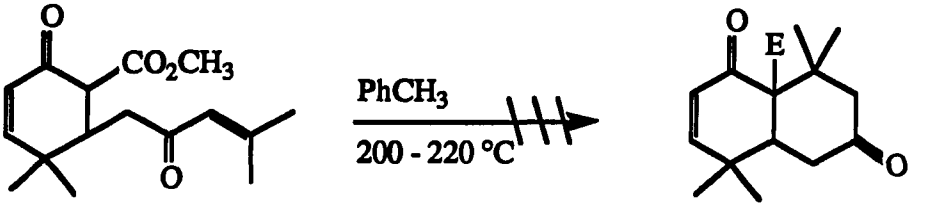
mixtures of cis and trans isomers. Usually 30% of the mixture was the enol form of the β-keto ester. The Michael adducts **67** and **68** were also used in a model study of the feasibility of the oxy-ene reaction.[29] Neither the thermal (heating ≥ 200 °C) nor the Lewis acid catalized oxy-ene reaction promoted the formation of **70** or **71**. Considering the



68 **70**



68 **70**

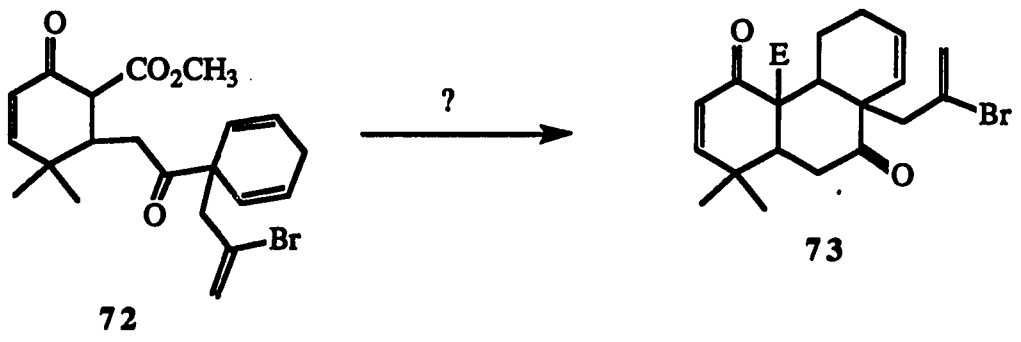


67 **71**

E = CO_2 CH_3

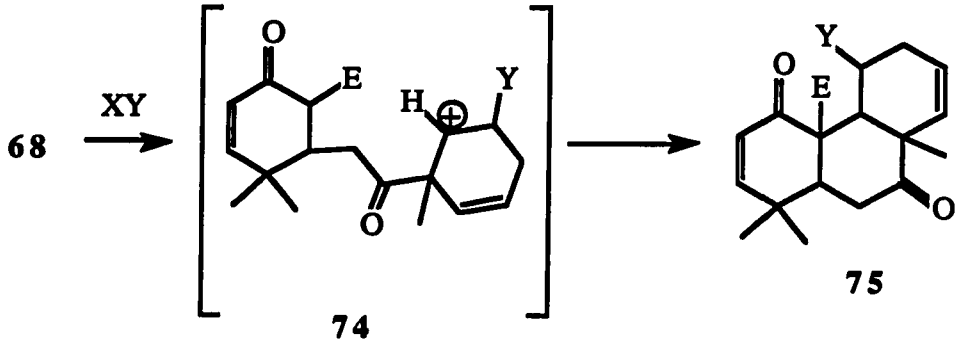
failure to effect an oxy-ene reaction plus the uncertainty of the composition of the keto-enolsilyl ether **54**, the strategy for the synthesis of kaurenoid natural products was changed.

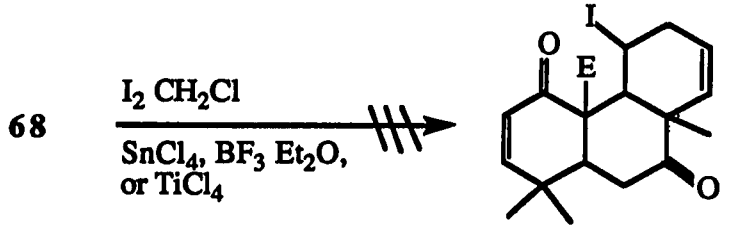
If a bromopropenyl group was substituted for the methyl group on the Michael adduct



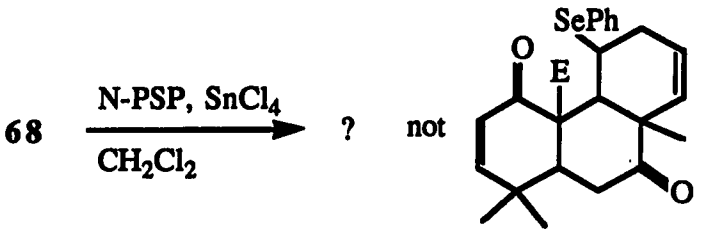
72 73

68, the synthesis is reduced to cyclizing **72** to the tricyclic intermediate **73**. Michael adduct **68** was employed as a model system for the cyclization. First a reversible carbocation cyclization was attempted. The carbocation **74** was expected to react with the acidic β-keto ester to form the tricyclic ring system. None of the reaction conditions employing iodine and a Lewis acid afforded the expected cyclized product. Nicolaou and

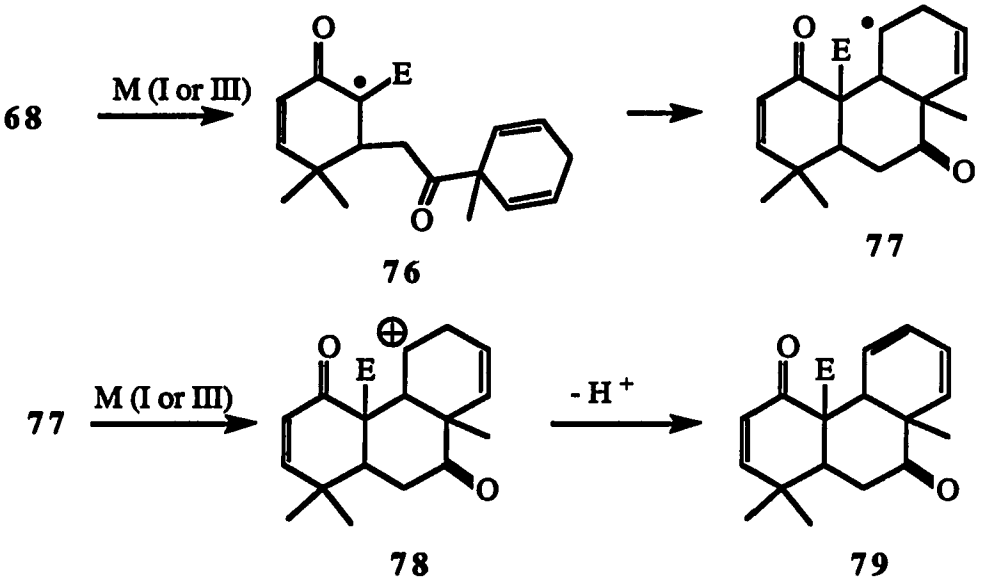




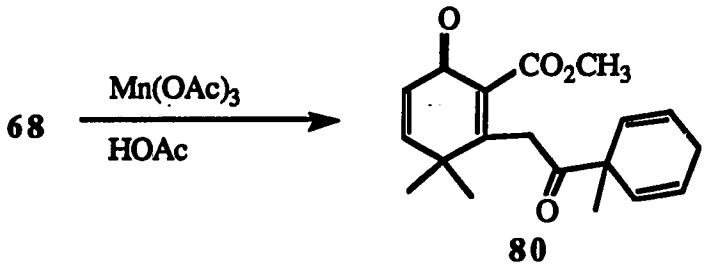
coworkers have reported the use of N-phenylseleno-phthalimide (NPSP) / $SnCl_4$ as a promoter of cyclizations in certain systems.[30] NPSP is not as reactive as other selenium reagents and is also sterically demanding because of the phthalimide moiety. In our case NPSP did not afford the expected product, but new and unidentifiable products were formed.



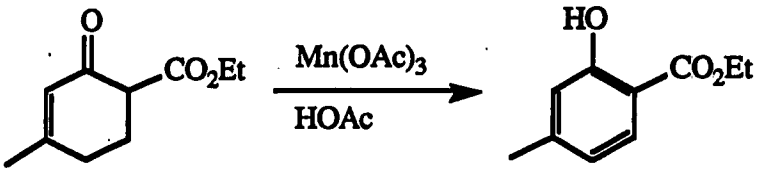
Next a radical cyclization was studied. There have been reports of the formation of radicals of the type **76** using manganese (III)[31, 32] or silver (I)[33] salts. The radical formed could



then add to the double bond forming **77** which could be oxidized by a second equivalent of the salt to give a carbocation **78**. Carbocation **78** could then lose a proton to form diene **79**. The standard reaction conditions [$Mn(OAc)_3$ / HOAc] failed in this system. The enone **80** was believed to have been formed in low yield, since phenol **82** was produced when β-keto ester **81** was submitted to the standard reaction conditions. The



80

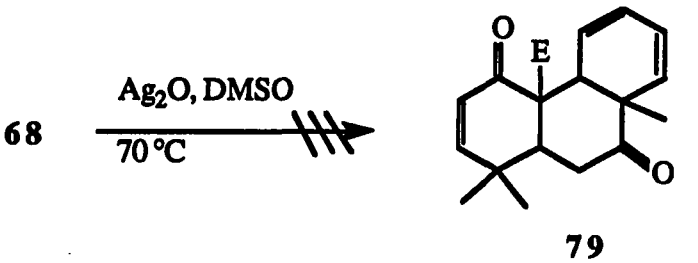


82 **81**

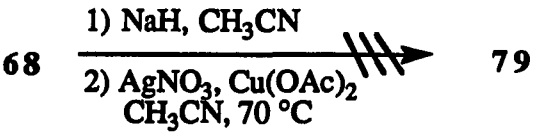
failure of the reaction may have been due to an equilibrium between **77** and **78** that favors **77**. Therefore copper (II) acetate was added as a co-oxidant. Copper (II) acetate is known to oxidize carbon radicals to carbocations more readily than other metal salts. This addition did not promote the cyclization to the tricyclic ring system. Next, silver salts were tried. Either using standard conditions (Ag_2O / DMSO, Δ) or conditions involving enolate formation (NaH, $AgNO_3$, $Cu(OAc)_2$)[34] did not result in the formation of the desired tricyclic ring system **80**.

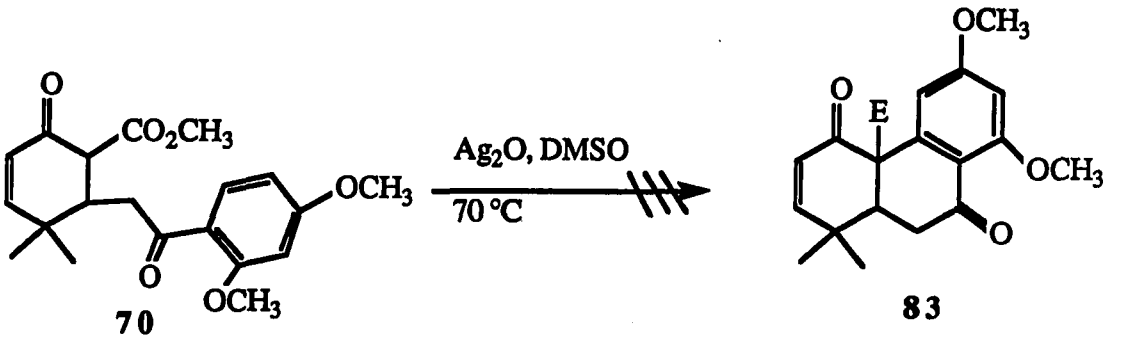
Snider and coworkers have reported the intramolecular cyclization of β-keto ester

radicals to electron-rich benzene rings.[35] The cyclization was attempted with Michael adduct **69** using Manganese (III) and silver (I) salts, but the tricyclic product **83** did not form, probably because the acetophenone moiety deactivated the benzene ring.

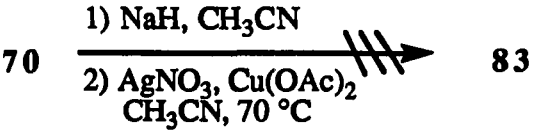


79

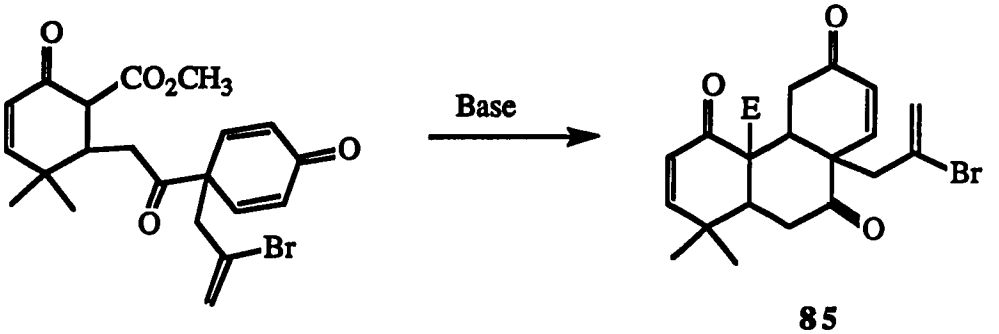




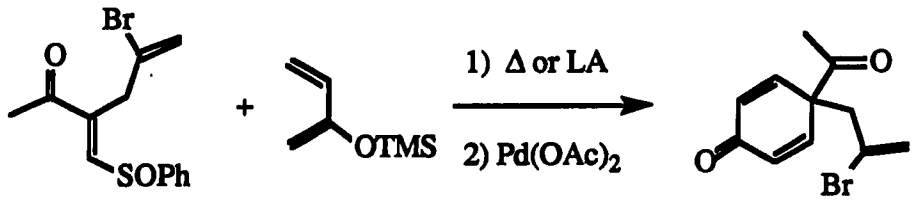
70 **83**



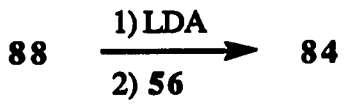
With the failures of the carbocation and radical cyclizations, an anionic route has been devised, but has yet to be tested. This route is centered around an intramolecular Michael addition of **84** to form the tricyclic product **85**. This intermediate was envisioned to be available from a Diels-Alder reaction between enone **86** and 2-trimethylsilyloxy-1,3-butadiene (**87**). Enone **86** will be synthesized following a method developed by Baraldi and coworkers.[36] The Diels-Alder adduct will then be oxidized to the dienone **88** by an Ito and coworkers reaction.[37] Dienone **88** will be used as a Michael donor to form the precursor **84** to the Michael addition. After cyclization to the tricyclic intermediate **85** the



84 **85**



86 87 88



bicyclo [3.2.1] octene ring system will be prepared by a vinyl radical cyclization which should provide our key tetracycic intermediate **58**. This intermediate will be used to synthesize a variety of kaurenoid natural products using known functional group manipulations.

EXPERIMENTAL

General

Unless otherwise stated, reagents used were purchased from commercial suppliers and were not purified unless stated. Dry diethyl ether and tetrahydrofuran were distilled from benzophenoneketyl, benzene was distilled from lithium aluminum hydride, methylene chloride and acetonitrile were distilled from calcium hydride, and toluene was distilled from sodium. Unless otherwise noted, all reactions were conducted in an argon atmosphere. For reactions requiring anhydrous conditions, the apparatus was flamed dried under a stream of argon. Melting points were determined using a Fisher-Johns melting point apparatus and are uncorrected. Silica gel used for flash chromatography was EM Science Kieselgel 60 (230-400 mesh) or Mereck 60 grade (230-400 mesh). Thin layer chromatography was performed using EM Science Kieselgel F_{254} prepared plates with thickness of 0.25 cm. The solvent systems were suitable mixtures of hexanes (H) and ethyl acetate (EA). High field proton nuclear magnetic resonance spectra were obtained at 300 MHz using Nicolet Magnetics Corporation 1280 spectrometer. All chemical shifts are reported in δ relative to tetramethylsilane as an internal standard. Coupling constants (J) are reported in Hz. Splitting patterns are designated: s (singlet), d (doublet), t (triplet), q (quartet), bs (broad singlet), m (multiplet) ABq (AB quartet). Carbon-13 nuclear magnetic resonance spectra were recorded at 75.46 MHz using a Nicolet Magnetics Corporation 1280 spectrometer and are reported in δ relative to the central peak of $CDCl_3$ (77.06 ppm). Infrared spectra were recorded using a Perkin-Elmer 1320 infared spectrophotometer and are reported in cm^{-1}. EI and CI (using the gas reported) low resolution mass spectra were recorded on a Finnegan 4023 mass spectrometer. High resolution mass spectra were

recorded using a Kratos model MS-50 spectrometer

1- (2-Bromo-2-propenyl)-4-cyclohexen-3-one-1-carboxylic acid **60**

To the *m*-anisic acid **59** (7.61g, 50 mmol) suspended in THF (40 mL) / NH_3 (160 mL) at -78 °C, was added in small pieces Li (0.83g, 120 mmol) until a blue color persisted. The mixture was then stirred an additional 25 min to which 2,3-dibromo-1-propene (6.20 mL, 60 mmol) was added dropwise over 10 min (solution changed from blue to yellow to orange to white). The mixture was stirred for 15 min at -78 °C, then solid NH_4Cl was cautiously added in three portions. Ammonia was removed under a stream of N_2 while warming to ambient temperature. The residue was dissolved in H_20 and washed twice with 100 mL Et_2O. The aqueous layer was cooled to 0 °C, then carefully acidified to pH 4 with cold concentrated HCl. The aqueous layer was extracted thrice with 200 mL of $CHCl_3$ and dried over Na_2SO_4. The chloroform solution was concentrated *in vacuo* to yield 14.1 g (103 %) of crude product which was dissolved in 40 mL of THF. To this solution was added 10% HCl (16.13 mL, 50 mmol), and the mixture was stirred for 2 h at ambient temperature. The solution was concentrated and 200 mL of Et_2O was added. A precipitate formed immediately which was filtered to yield 8.74 g (67 %). The melting point was 176 - 178 °C. NMR (D_6 acetone) δ 2.82 – 3.05 (m, 4 H), 5.59 (d, J = 1.8 Hz 1 H), 5.76 (m, 1 H), 5.92 (dd J = 10.2 Hz, 2.7 Hz, 1 H), 6.98 (ddd, J = 10.2 Hz, 3.0 Hz, 5.4 Hz, 1 H). ^{13}C NMR (D_6 Acetone) 34.70, 45.15, 48.70, 40.06, 122.03, 127.81, 129.31, 147.34, 175.09, 195.96 ppm. Low resolution mass spectrum m/e: 55, 77, 95, 109, 179, 213, 215, 240, 242, 258, 259, 260, 261; High resolution mass spectrum for $C_{10}H_{11}BrO_3$ requires 257.98915, measured 257.98915.

Methyl 1-(2-bromo-2-propenyl)-4-cyclohexen-3-one-1-carboxylate **60a**

To a solution of the acid **60** (8.41 g, 32.46 mmol) in a 2 : 1 solution of CH_2Cl_2 : Et_2O (165 mL) separated in 5 lots was added diazomethane until the evolution of N_2 gas had ceased. The solution was concentrated under a stream of N_2, and the residue was purified by flash chromatography eluting with 2 : 1 Hex : EA to yield **60a** 8.87 g (83 %) as a light yellow solid. TLC (3 : 1 H : EA) $R_f = 0.21$. ^1H NMR ($CDCl_3$) δ 2.45 - 2.60 (m, 2 H), 2.80 - 3.00 (m, 4 H), 3.69 (s, 3 H), 5.58 (s, 2 H), 6.00 - 6.07 (dt, J = 1.8 Hz, 10.2 Hz, 1 H), 6.85 - 6.92 (m, 1H). ^{13}C NMR ($CDCl_3$) δ 33.98, 44.85, 48.35, 48.35, 48.60, 52.62, 121.93, 129.80, 146.71, 174.21, 196.24. IR ($CDCl_3$) 3150, 2990, 2950, 2900, 1810, 1792, 1730, 1680, 1621, 1437, 1385, 1212 cm^{-1}. Low resolution mass spectrum: m/e 59, 68, 79, 105, 121, 133, 193, 213, 215, 242, 243, 272, 274. High resolution mass spectrum for $C_{11}H_{13}BrO_3$ requires 272.00480, measured 272.00466.

Methyl 6-methylene-3-oxo-bicyclo [3.2.1] octane-1-carboxylate **54**

To a solution of the ester **60a** (5.0 g, 18.31 mmol) in dry benzene (180 mL) at 80 °C was added a solution of *n*-Bu_3SnH (5.91 mL, 21.97 mmol) and AIBN (0.30 g, 1.83 mmol) in benzene (40 mL) over 2 h. The solution was stirred an additional 1 h, then the benzene was removed *in vacuo*. The residue was dissolved in 85 mL of Et_2O to which 35 mL of H_2O and $KF{\cdot}2H_2O$ (8.24 g, 87.55 mmol) was added. The mixture was vigorously stirred overnight. The mixture was separated and washed twice with 50 mL of H_2O, 50 mL of brine and dried over Na_2SO_4. The ethereal solution was concentrated *in vacuo*, and the residue was purified by flash chromatography using Florisil and eluting with hexanes to afford 2.52 g (71%) of **54**. TLC (3 : 1 H : EA) R_f = 0.27. ^1H NMR ($CDCl_3$) δ. ^{13}C

NMR ($CDCl_3$) δ 40.79, 41.31, 41.85, 49.73, 50.31, 50.61, 52.26, 108.89, 150.36, 174.80, 208.23; IR ($CHCl_3$) 3020, 2960, 1730, 1718, 1662, 1437, 1258, 1230, 1069, 900 cm^{-1}. Low resolution mass spectrum: m/e 39, 53, 77, 91, 107, 119, 135, 151, 162, 194. High resolution mass spectrum for $C_{11}H_{14}O_3$ requires 194.09429, measured 194.09465.

Methyl 3-(*t*-butyldimethylsilyloxy)-6-methylene-
bicyclo [3.2.1] oct-2-ene -1-carboxyxlate **55** and **65**

To a solution of the ketone **54** (2.05 g, 10.55 mmol) in CH_2Cl_2 at 0 °C was added N,N-diisopropylethylamine (3.59 mL, 20.60 mmol) followed by dropwise addition of TBSOTf (2.72 mL, 11.85 mmol). The solution was slowly warmed to ambient temperature 16 h. The CH_2Cl_2 was removed *in vacuo* and hexanes were added. The precipitate was removed by filtering through Celite, then concentrated. The mixture was purified by flash chromatography using 6 : 1 H : EA to yield 0.59 g (93 %) of a mixture of **55** and **65**. TLC (6 : 1 H : EA) R_f = 0.47. ^1H NMR ($CDCl_3$) δ 0.12 (s, 4.8 H), 0.14 (s, 1.2 H), .90 (s, 7.2 H), .93 (s, 1.8 H), 1.70 - 2.22 (m, 4 H), 2.40 - 2.55 (m, 2 H), 2.60 - 2.80 (m, 2 H), 2.91 (dd, J = 6.9 Hz, 4.5 Hz, 1 H), 4.54 (s, 0.8 H), 4.74 (s, 0.8 H), 4.94 (s, 0.2 H) 5.03 (s, 0.8 H), 5.05 (s, 0.2 H), 5.32 (s, 0.2 H). ^{13}C NMR ($CDCl_3$) δ 18.02, 25.69, 41.20, 41.97, 41.85, 48.67, 52.01, 101.60, 107.92, 109.40, 110.0, 148.26, 155.38, 176.60. IR ($CHCl_3$) 3030, 2930, 2860, 1720, 1718, 1655, 1360, 1200, 1150, 835, 780, 680 cm^{-1}. Low resolution mass spectrum: m/e 45, 59, 73, 89, 105, 117, 191, 251, 267, 308.

Ethyl 3-(*t*-butyldimethylsilyloxy)-1-(2-carboxylate-1-ethanone)-6-methylene-2-bicyclo [3.2.1] octene **63** and **64**

To a solution of LDA [prepared by the addition of *n*-BuLi (0.96 mL, 2.35 mmol) to a solution of diisopropylamine (0.36 mL, 2.57 mmol) in 5 mL of dry THF at O °C] at -94 °C, was added a solution of ethyl acetate (0.21 mL, 2.14 mmol) in 1 mL of dry THF over 10 min. The solution was stirred at -94 °C for 15 min, then warmed to -78 °C. A solution of the mixture of **63** and **64** (300 mg, 0.97 mmol) in 2.5 mL of dry THF was added over 15 min. The solution was warmed slowly to ambient temperature and was quenched with 1 mL of saturated NH_4Cl. The THF was removed *in vacuo*, and the residue was diluted with 20 mL of Et_2O. The ethereal solution was washed twice with 10 mL of H_2O, 10 mL of brine and dried over Na_2SO_4. The crude product was purified by flash chromatography eluting with 3 : 1 H : EA to yield 244 mg (69%) of a mixture of **63** and **64**. TLC (6 : 1 H : EA) R_f = 0.47. ^1H NMR ($CDCl_3$) δ 0.12 (s, 6 H), 0.90 (s, 9 H0, 1.28 (t, J = 7.2 Hz, 3 H), 1.60 - 2.25 (m, 3 H), 2.40 - 3.00 (m, 4 H), 3.52 (s, 0.8 H), 3.72 (s, 1.2 H), 4.20 (q, J = 7.2 Hz, 2 H), 4.53 (bs, 0.4 H), 4.68 (bs, 0.6 H0, 4.74 (bs, 0.4 H), 4.89 (bs, 0.6 H), 4.90 - 5.10 (m, 1 H). IR ($CHCl_3$) 3060, 2940, 2860, 1735, 1710, 1655, 1470, 1460, 1360, 1200, 870, 780 cm^{-1}. Low resolution mass spectrum: m/e 59, 73, 89, 117, 191, 237, 251, 265, 308, 322, 364.

General Procedure for Michael Additions

To a solution of LDA (1.2 equivalents) in dry THF at - 78 °C, was added dropwise over 15 min a solution of the methyl ketone (1.1 equivalents) in dry THF. The solution was stirred for 20 min at - 78 °C. A solution of **56** (1 equivalent) in dry THF was added dropwise to the solution and stirred for 45 min at - 78 °C. The solution was warmed to

ambient temperature and quenched by the addition of excess saturated NH_4Cl. The mixture was extracted thrice with 10 mL of Et_2O. then washed with 20 mL of brine and dried over Na_2SO_4. The crude product was purified by flash chromatography.

Adduct **66**

TLC (2 : 1 H : EA) R_f = 0.43. ^1H NMR ($CDCl_3$) δ 1.0 - 1.40 (m, 6 H), 2.60 - 3.50 (m, 4 H), 3.70, (s, 1.5 H), 3.72 (s, 0.9 H), 3.78 (s, 0.6 H), 5.80 - 6.00 (m, 1 H), 6.60 - 6.80 (m, 1 H), 7.30 - 7.70 (m, 3 H), 7.85 - 8.00 (m, 2 H), 11.94 (s, 0.2 H). IR ($CHCl_3$) 3000, 2950, 1735, 1710, 1670, 1605, 1450, 1460, 1260, 845 cm^{-1}. Low resolution mass spectrum: m/e 51, 77, 105, 121, 149, 181, 199, 225, 253, 268, 300.

Adduct **67**

TLC (3 : 1 H : EA) R_f = 0.25. ^1H NMR ($CDCl_3$) δ 1.0 - 1.29 (m, 6 H), 1.88 (s, 1 H), 1.90 (s, 2 H), 2.13 (s, 1 H), 2.14 (s, 2 H), 2.25 - 3.50 (m, 4 H), 3.33, (s, 0.6 H), 3.34 (s, 0.4 H), 3.68 (s, 0.6 H), 3.71 (s, 1 H), 5.80 - 6.10 (m, 2 H), 6.39 (d, J = 10.1 Hz, 0.34 H), 6.72 (d, J = 10.1 Hz, 0.76 Hz), 7.30 - 7.70 (m, 3 H), 11.97 (s, 0.34 H). IR ($CHCl_3$) 2950, 2920, 1730, 1675, 1612, 1440, 1380, 1355, 1232, 900, 730 cm^{-1}. Low resolution mass spectrum: m/e 51, 77, 105, 121, 149, 181, 199, 225, 253, 268, 300.

Adduct **68**

TLC (2 : 1 H : EA) R_f = 0.29. ^1H NMR ($CDCl_3$) δ 0.8 - 1.80 (m, 9 H), 2.20 - 3.60 (m, 6 H), 3.69 (s, 2 H), 3.72 (s, 1 H), 5.50 - 5.60 (m, 2 H), 5.75 - 5.95 (m, 3 H), 6.70 (d, J = 10.1 Hz, 0.67 H), 7.10 (d, J = 10.1 Hz, 0.33 Hz), 11.94 (s, 0.33 H). IR

($CHCl_3$) 3010, 2970, 2930, 1720, 1670, 1615, 1510, 1460, 1380, 1355, 1225, 1160, 1120, 1090 cm^{-1}.

Adduct **69**

TLC (2 : 1 H : EA) R_f = 0.27. ^1H NMR ($CDCl_3$) δ 1.00 - 1.20 (m, 6 H), 2.64 (dd, J = 14.8 Hz, 5.7 Hz, 0.3 Hz, 0.3 H), 2.96 (dd, J = 17.8 Hz, 5.5 Hz, 0.7 H), 3.06 - 3.72 (m, 3 H), 3.58 (s, 2 H), 3.62 (s, 1 H), 3.85 (s, 4 H), 3.89 (s, 2 H), 5.85 - 6.02 (m, 2 H), 6.42 - 6.56 (m, 2 H), 6.62 (d, J = 10.1 Hz, 0.3 H), 6.74 (d, J = 10.1 Hz, 0.7 Hz), 7.38 (d, J = 8.8 Hz, 0.7 H), 7.83 (d, J = 8.8 Hz, 0.3 H) 11.97 (s, 0.3 H). IR ($CHCl_3$) 3000, 2960, 2840, 1740, 1650, 1600, 1498, 1460, 1420, 1260, 1240, 1060, 1030, 840, 830 cm^{-1}. Low resolution mass spectrum m/e 41, 53, 77, 91, 107, 122, 149, 165, 180, 207, 313, 345, 360. High resolution mass spectrum for $C_{20}H_{24}O_6$ requires 360.15729, measured 360.15719.

REFERENCES

1. For a review of diterpene natural products, see: McCrindle, R.; Overton, K.H. *Rodd's Chemistry of Carbon Compounds*, 2nd ed, Coffey, S., Ed., New York, **1969**, Vol. II, part C, pp 373 - 402.
2. Briggs, L. H.; Cawley, R. W.; Loe, J. A.; Taylor, W. I. *J. Chem. Soc.* **1950**, 955.
3. Djerassi, G.; Cais, M.; Mitschen, L. A. *J. Am. Chem. Soc.* **1959**, *81*, 2386.
4. Cross, R. H. B.; Gult, ; Hanson, J. R. *J. Chem. Soc.* **1963**, 2944
5. Cross, B. E. *J. Chem. Soc.* **1963**, 2937.
6. Perezamador, M. C.; Jiminez, F. G. *Tetrahedron* **1966**, *22*, 1937.
7. Hedden, P.; MacMillan, J.; Phinney, B. O. *Annu. Rev. Plant Physiol.* **1978**, *29*, 149.
8. Perezamador, M. C.; Jiminez, F. G.; Herran, J.; Flores, S. E. *Tetrahedron* **1964**, *20*, 2999.
9. Wenkert, E. *Chem. Ind. (London)* **1955**, 282.
10. Hanson, J. R. *Forschr. Chem. Org. Naturst* **1971**, *29*, 395.
11. a) Sheeter, I.; West, C. A. *J. Biol. Chem.* **1969**, *244*, 3200. b) Fall, R. R.; West, C. A. *J. Biol. Chem.* **1971**, *246*, 6913.
12. Coates, R. M.; Cavender, P. L. *J. Am. Chem. Soc.* **1980**, *102*, 6358.
13. Turner, R. B.; Ganshirt, K. H. *Tetrahedron Lett.* **1961**, 231.
14. Turner, R. B.; Shaw, P. E. *Tetrahedron Lett.* **1960**, No. 18, 24.
15. Bell, R. A.; Ireland, R. E.; Partyka, R. A. *J. Org. Chem.* **1962**, *27*, 3741.
16. Bell, R. A.; Ireland, R. E.; Mander, L. N. *J. Org. Chem.* **1966**, *31*, 2536.
17. Church, R. F.; Ireland, R. E.; Marshall, J. A. *J. Org. Chem.* **1966**, *31*, 2530.

18. Masamune, S. *J. Am. Chem. Soc.* **1964**, *86*, 288.

19. Masamune, S. *J. Am. Chem. Soc.* **1964**, *86*, 289.

20. Masamune, S. *J. Am. Chem. Soc.* **1964**, *86*, 290.

21. Masamune, S. *J. Am. Chem. Soc.* **1964**, *86*, 291.

22. Kitadani, M.; Ito, K.; Yoshikoshi, A. *Bull. Chem. Soc. Japan* **1971**, *44*, 3431.

23. Tahara, A.; Shimagaki, M.; Ohara, S.; Nakata, T. *Tetrahedron Lett.* **1973**, 1701.

24. Corey, E. J.; Wess, G.; Xiang, Y. B.; Singh, A. K. *J. Am. Chem. Soc.* **1987**, *109*, 4717.

25. Marinovic, N. M.; Ramanathan, H. *Tetrahedron Lett.* **1983**, *24*, 1871.

26. For a review of trialkylsilyl triflourosulfonates, see: Emde, H.; Domsch, D.; Feger, H.; Frick, U.; Gotz, A.; Hergott, H. H.; Hoffman, K.; Kober, W.; Krageloh, K.; Oesterle, T.; Steppan, W.; West, W.; Simchen, G. *Synthesis* **1982**, 1.

27. Huang, B. S.; Parish, E. J.; Miles, D. H. *J. Org. Chem.* **1974**, *39*, 2647.

28. Lin, H. -J.; Browne, E. N. C. *Can. J. Chem.* **1981**, *59*, 601.

29. For a review of the ene reaction, see: Oppolzer, W. *Angew. Chem. Int. Ed. Engl.* **1978**, *17*, 476.

30. Nicolaou, K. C.; Claremon, D. A.; Barnette, N. E.; Seitz, S. P. *J. Am. Chem. Soc.* **1979**, *101*, 3704.

31. Dessau, R. M.; Heiba, E. I. *J. Org. Chem.* **1974**, *39*, 3456.

32. Corey, E. J.; Ghosh, A. K. *Chemistry Lett.* **1987**, 223.

33. Ito, Y.; Fujii, S.; Konoike, T.; Saegusa, T. *Synthetic Commun.* **1976**, *6*, 429.

34. Kraus, G. A.; Applegate, J. M.; Johnston, B. E. Chemistry Dept., Iowa State University, manuscript in preparation.

35. Snider, B. B.; Mohan, R.; Kates, S. A. *J. Org. Chem.* **1985**, *50*, 3659.

36. Baraldi, P. G.; Barco, A.; Benetti, S.; Pollini, G. P.; Zanirato, V. *Tetrahedron Lett.* **1984**, *25*, 4291.

37. Ito, Y.; Hiro, T.; Saegusa, T. *J. Org. Chem.* **1978**, *43*, 1011.

PART III: AN APPROACH TO ISOCEDRANE NATURAL PRODUCTS USING A BRIDGEHEAD CARBOCATION

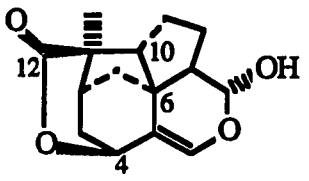
INTRODUCTION

This manuscript will describe the synthetic program directed toward the synthesis of trixikingolide, an isocedrane natural product. The route uses a bridgehead carbocation to construct an advanced intermediate. The key step in the synthesis is a regioselective aldol condensation reaction to construct the cis fused five membered ring common in this class of natural products. The testing of this route is still in the infant stages, so this is only a preliminary communication.

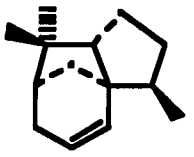
HISTORICAL

Trixikingolide Natural Products

The trixikingolides **1** are a family of natural products that are earmarked by an unusual bicyclic ring system related to isocederene **2**. The pentacyclic ring system of the



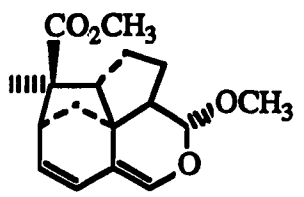
1



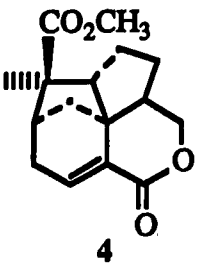
2

trixikingolides contains a central bicyclo [3.2.1] octane unit with a cis fused five membered ring at carbons 6 and 10, and a six membered ring containing an enol acetal. The fifth ring is a lactone that bridges carbons 4 and 12. Many examples of trixikingolide natural products have been isolated and characterized. The discovery of this class was due entirely to Bohlman and coworkers in their chemotaxological investigation of *Nassauvinea* , a subtribe of the tribe *Mutisieae*. In their study of many genera of this tribe, Bolhmann discovered that the aerial parts contained unusual highly oxygenated isocederene type natural products. This class of natural products was called trixikingolides. There are many examples in this class; such as, trixikingolide **1** isolated from *Trixis compostia*,[1,2] ester diene **3** isolated from *Trixis vantheric*,[3] ester lactone **4** isolated from *Gungia stuebii*,[4] diacetate **5** isolated from *Moscharia pinnatitida*,[5] triacetate **6** isolated from *Pronstia cuneifolic* Don *formamendocina*,[6] and the trixikingolide **7** isolated from *Perezia multiflora*.[7]

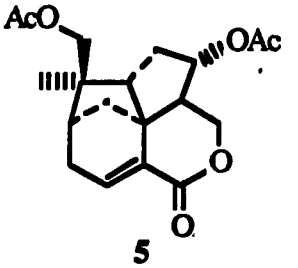
The biosynthetic pathway of isocederene natural products has to this date not been elucidated, but many groups have proposed the pathway outlined in Scheme I.[1,8,9] The



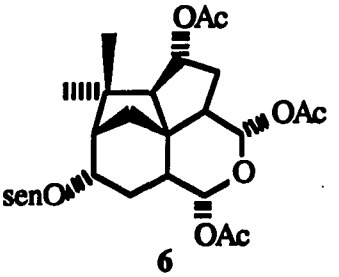
3



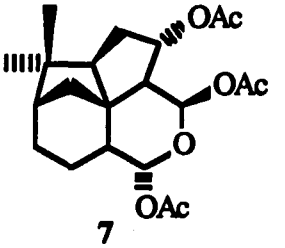
4



5

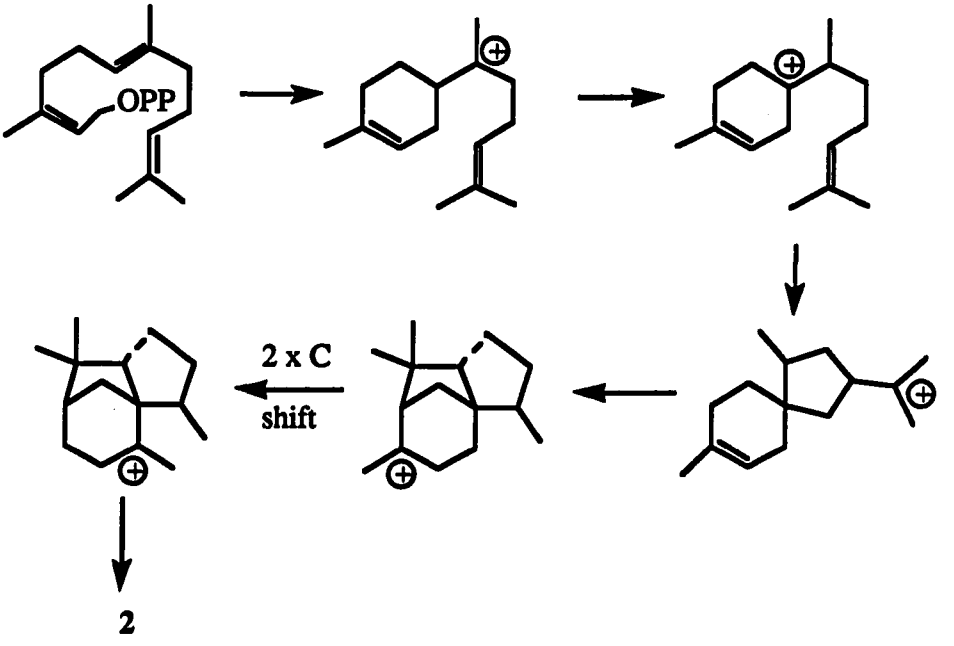


6



7

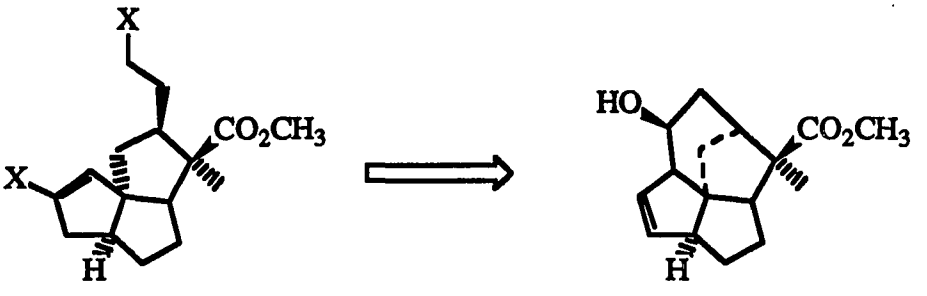
Scheme I



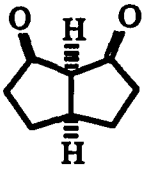
2

only uncertainity of this pathway is the unusual 1,2 carbon shifts that are needed to prepare isocederane.

The synthesis of angular fused sesquiterpenes has been an active area of research, but there have not been any reports of the total synthesis of trixikingolide. Paquette[10] and Cheney[11] have reported an attempted synthesis of trixikingolide. Their approach was centered around an intramolecular alkylation to form the central bicyclo [3.2.1] octane unit from the tricyclic precursor **8**. They were never successful in the cyclization of **8** to form tetracycle **9**. Paquette and Cheney prepared a variety of precursors for the cyclization starting with diketone **10**. Their first attempt was using a Prins reaction on aldehyde **11**.

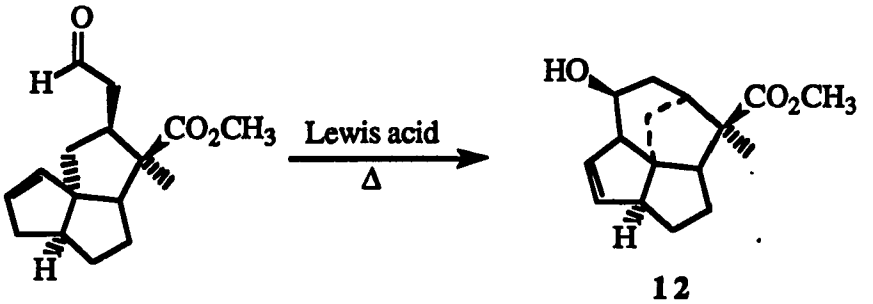


8 **9**

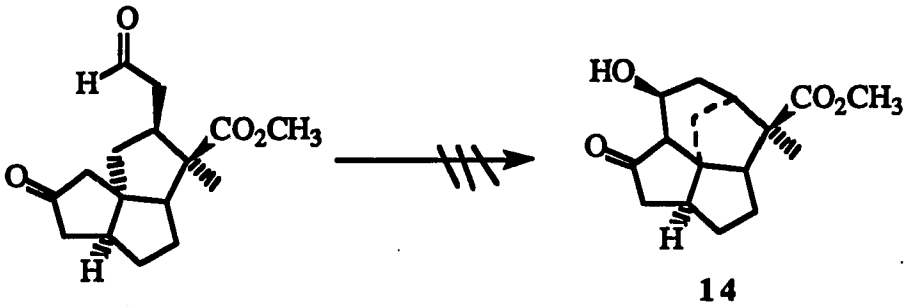


10

Heating **11** with a variety of Lewis acids did not provide the cyclized product **12**. They also tried an aldol condensation to effect the cyclization. Using ketone **13** in both basic and acidic reaction conditions, aldol product **14** was not obtained. An initial alkylation to form

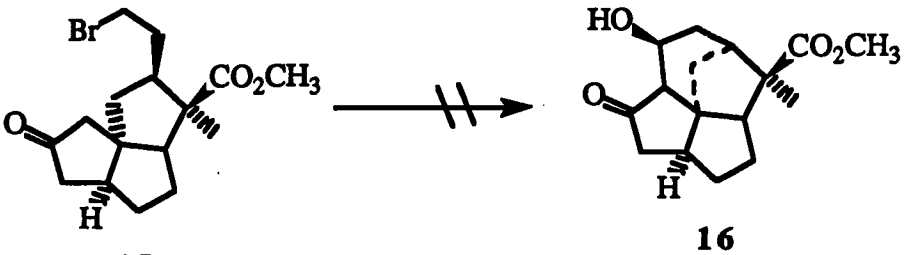


11 12

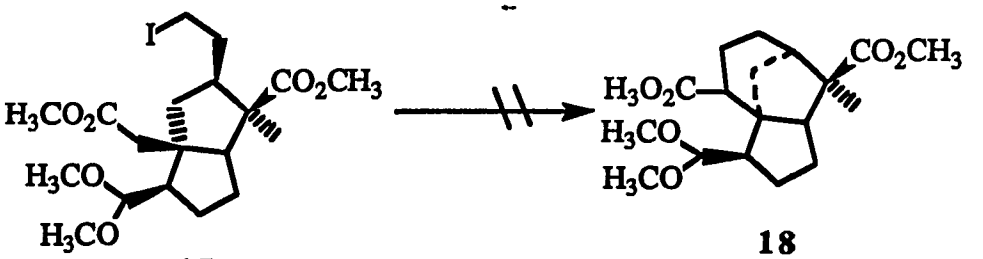


13 14

the bicyclo [3.2.1] octane moiety followed by an aldol condensation strategy was also attempted. An intermediate in the synthesis of **13** was converted to the ketone **15**, but

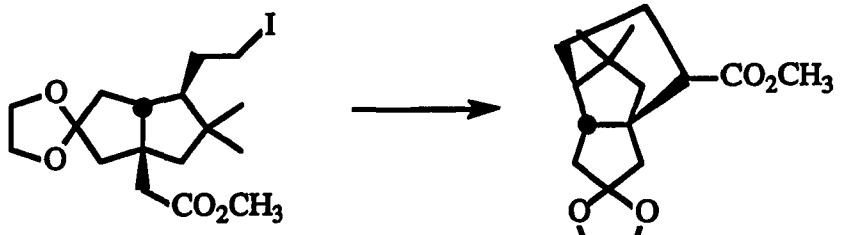


15 16



17 18

none of the alkylation conditions employed resulted in the formation of **16**. Ester **17** was also prepared, and like **15** none of the cyclized product was detected. Both Paquette and Cheney concluded that the cyclization of **13**, **15**, and **17** failed due to unattainable reaction trajectories and proximity effects even though there was precedent for such a cyclization. Danishefsky and coworkers were successful in the intramolecular alkylation of **19** to afford **20**.[12]

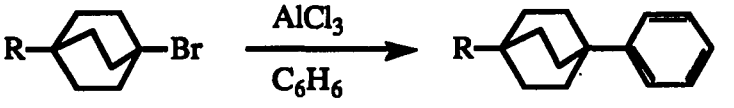


19 **20**

Bridgehead Carbocations in Organic Synthesis

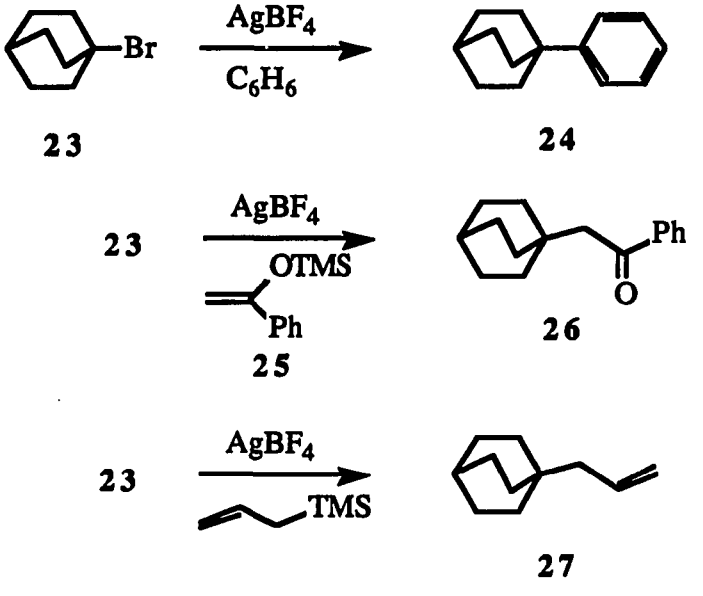
Bridgehead carbocations have the potential to be powerful intermediates in organic sythesis. These carbocations have been extensively studied in the physical organic community, and these results have been tabulated.[13] The potential of these intermediates is due to the lack of rearrangements generally found in smaller bicyclic ring systems, and stereoselective additions to these intermediates. The use of bridgehead carbocations in organic synthesis has not been extensively explored. The thrust of the work has been reported in a review by Kraus and coworkers.[14]

One of the first examples was a report by Gray and Kelly,[15] who employed bridgehead bromides in a Friedel-Crafts reactions. They found that treatment of bridgehead bromide **21** (R = alkyl) with aluminum trichloride and bromobenzene afforded **22**. Kraus



21 22

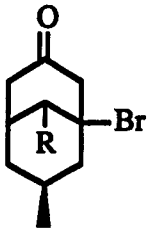
and Hon were also successful in generating bridgehead carbocations of bicyclo [2.2.2] octanes and reacting them with a variety of nucleophiles.[16] The carbocation from bridgehead bromide **23** was formed by the addition of silver (I) tetrafluoroborate in the presence of nucleophiles. When benzene was used as the nucleophile, **24** was obtained in 90% yield. Other nucleophiles reported were enol silyl ether **25** which afforded ketone **26** in 65% yield and allyltrimethylsilane which afforded **27** in 72% yield. They also reported the intramolecular version of this reaction. They employed bridgehead bromide **28**



and used allyltrimethylsilane as the trapping agent to form alkene **29** in 71% yield. Benzene and enol silyl ethers have been shown also to be suitable nucleophiles in this sequence.

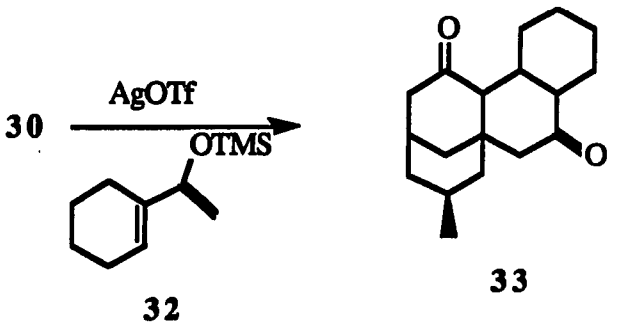
23 **29**

Kraus and Hon have been successful in forming bridgehead carbocations of bicyclo [3.3.1] nonanes.[17] Bridgehead bromides **30** and **31** reacted in a similar manner as bridgehead bromide **23**. Allyltrimethylsilane, amines, and enol silyl ethers were all suitable nucleophiles. They also discovered that diene **32** could be used as a nucleophile to afford **33**. One observation was the formation of appreciable amounts of bridgehead

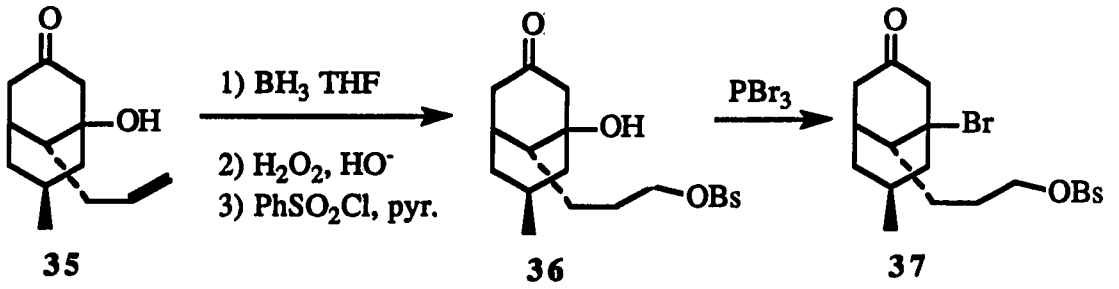


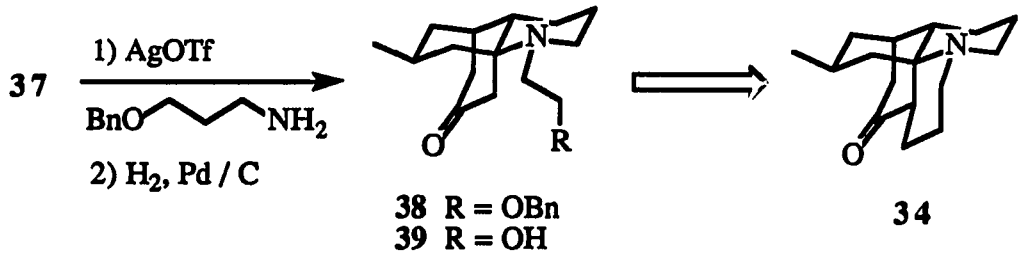
30 R = H
31 R = $CH_3CH{=}CH_2$

fluoride when silver (I) tetrafluoroborate was used, but this type of side product could be avoided with the use of silver (I) triflate. They have shown the utility of bridgehead carbocation chemistry in their direct synthesis of (±)-lycopodine **34**.[17,18] Kraus and



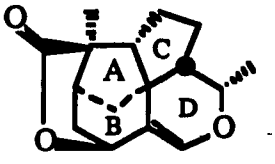
Hon regioselctively oxidized the alcohol **35** to a diol, then formed the benzene sulfonate **36**. The bridgehead bromide **37** was obtained by treatment of **36** with phosphorus tribromide. Bridgehead bromide **37** was converted to **38** using silver (I) triflate and 1-amino-3-benzyloxypropane. Kraus and Hon intersected with the synthesis of (±)-lypodine reported by Heathcock and coworkers[19] by the deprotection of the benzyloxy group to provide **39**.



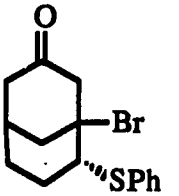


RESULTS AND DISCUSSION

In envisioning the synthesis of trixikingolide **1**,[1] bridgehead bromide **40** was predicted to be a key intermediate in the synthesis. The intermediate would allow for



1

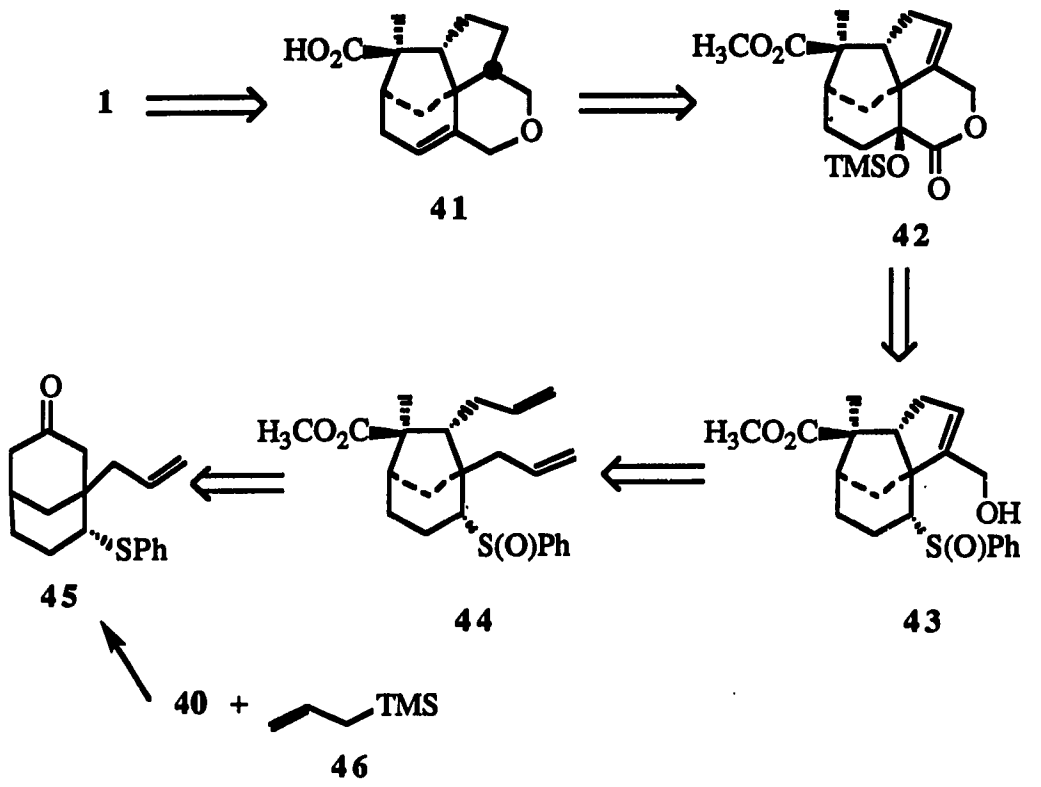


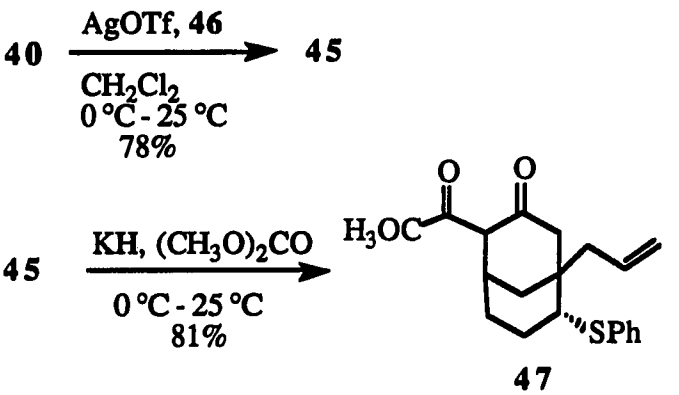
40

appendage of the C ring using bridgehead carbocation chemistry. Our approach is outlined retrosynthetically in Scheme II. The advanced intermediate **41** was envisioned to be available from **42** by hydrogenation, elimination of the trimethylsilyloxy group, and deesterification. Lactone **42** would be available from **43** by a Pummerer rearrangement,[20] followed by cyanohydrin formation and lactonation. The transformation of **44** to **43** is the key to our approach. After ozonolysis to form the dialdehyde, a regioselective aldol condensation must occur. Using molecular models, the aldehyde linkage at the bridgehead appears to be the most accessible to deprotonation which would afford **43** after reduction. Ester **44** will be synthesized from **43** by a Buchi ring contraction[21] followed by Michael addition of an allyl group and alkylation. Compound **45** is obtained from a bridgehead carbocation reaction with allyltrimethylsilane **46** serving as the nucleophile.

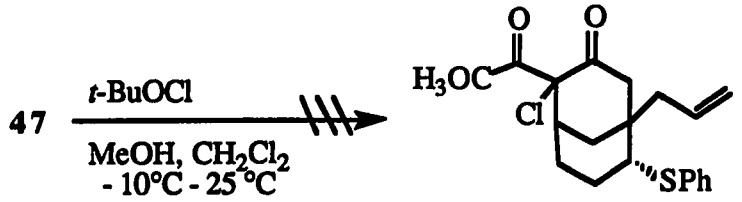
Starting the synthesis with bridgehead bromide **40**,[22] the bridgehead position was alkylated with allyltrimethyl silane in the presence of silver (I) triflate to afford **45** in 78% yield. Ketone **45** was carbomethoxylated by the addition of potassium hydride and

Scheme II.

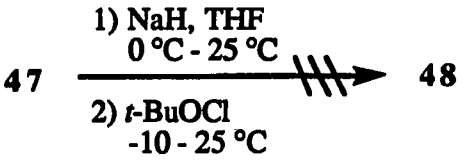

1
HO2C
O
41
H3CO2C
O
TMSO
O
42
H3CO2C
OH
S(O)Ph
43
H3CO2C
S(O)Ph
44
O
SPh
45
40 +
TMS
46


40
AgOTf, 46
CH2Cl2
0 °C - 25 °C
78%
45
45
KH, (CH3O)2CO
0 °C - 25 °C
81%
O
O
H3OC
SPh
47

dimethylcarbonate to provide β-keto ester **47** in 81% yield.[21] Now the stage was set for the Buchi ring contraction. The first step was the chlorination of the β-keto ester with *t*-butyl hypochlorite. In the case of **47**, this intermediate could not be chlorinated. The β-keto ester moiety was activated by the formation of the enolate with sodium hydride, but none of the chlorinated product **48** was produced. The failure of the reaction is

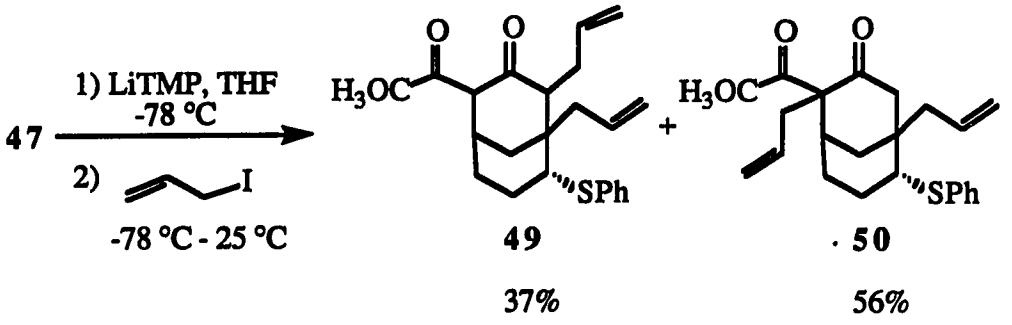


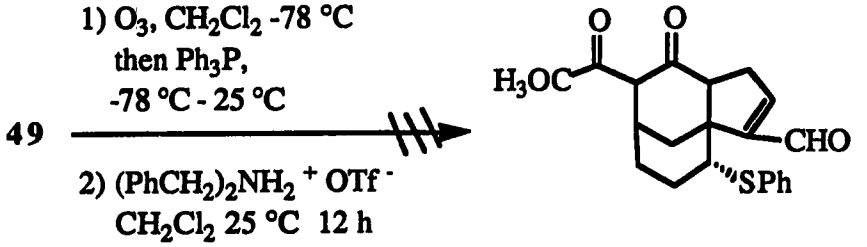
48



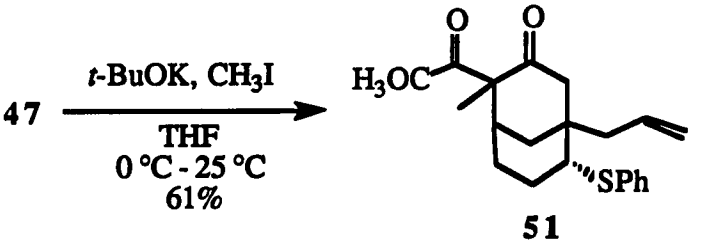
rationalized by the presence of the phenylthio group. There has been a report of the oxidation of a sulfide to a sulfoxide using *t*-butyl hypochlorite.[23]

At this point there were three different avenues to circumvent this problem. First the dianion of β–keto ester **47** could be formed and alkylated with allyl iodide. Second a photochemical ring contraction could be employed which had been previously reported for bicyclic ring systems.[24] Third the sulfoxide could be formed followed by the completion of the scheme. Formation of the dianion was accomplished by using 2.3 equivalents of lithium tetramethylpiperdinamide at -78 °C. Upon the addition of allyl iodide, a disappointing 1 : 1.5 mixture of **49** : **50** resulted which could be separable by chromatography. With the material in hand, the ozonolysis-aldol condensation sequence





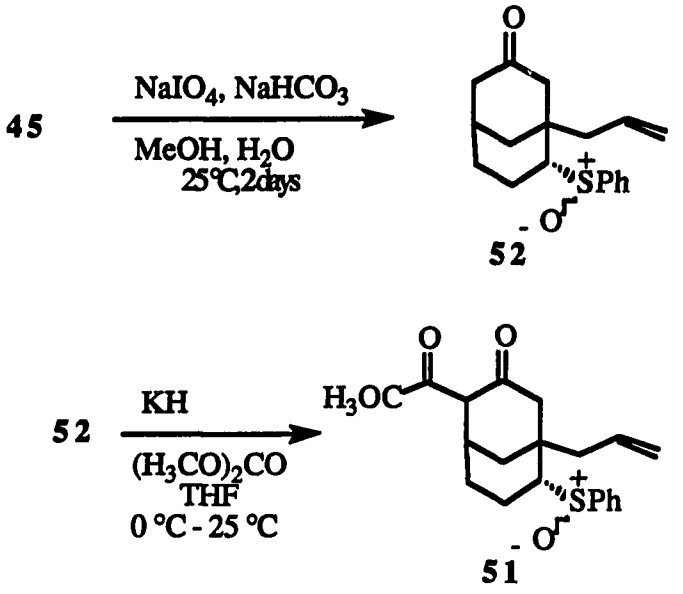
was attempted.[25] None of the desired product was detected in the reaction mixture. The photochemical avenue did not show any promise either. The β-keto ester was methylated with potassium *t*-butoxide and methyl iodide[24] to provide **51** in 61% yield. Irradiating **51**



with a Hanovia 450W medium presure mercury lamp did not afford the expected product, but desulfurization products might have been formed by NMR spectroscopy.

Compound **45** was oxidized with sodium periodate to yield **52** as a mixture of diastereomers that were not separable by flash chromatography in 87% yield. Sulfoxide

52 was then carbomethoxylated by deprotanation with potassium hydride and dimethylcarbonate to prepare **53** in 78% yield. This is our current point of progress in this area. β-Keto ester **53** has been chlorinated, but the conditions for the ring contraction have not been worked out at this point.



EXPERIMENTAL

General

Unless otherwise stated, reagents used were purchased from commercial suppliers and were not purified unless stated. Dry diethyl ether and tetrahydrofuran were distilled from benzophenoneketyl, benzene was distilled from lithium aluminum hydride, methylene chloride and acetonitrile were distilled from calcium hydride, and toluene was distilled from sodium. Unless otherwise noted, all reactions were conducted in a argon atmosphere. For reactions requiring anhydrous conditions, the apparatus was flamed dried under a stream of argon. Melting points were determined using a Fisher-Johns melting point apparatus and are uncorrected. Silica gel used for flash chromatography was EM Science Kieselgel 60 (230-400 mesh) or Mereck 60 grade (230-400 mesh). Thin layer chromatography was performed using EM Science Kieselgel F_{254} prepared plates with thickness of 0.25 cm. The solvent systems were suitable mixtures of hexanes (H) and ethyl acetate (EA). High field proton nuclear magnetic resonance spectra were obtained at 300 MHz using Nicolet Magnetics Corporation 1280 spectrometer. All chemical shifts are reported in δ relative to tetramethylsilane as an internal standard. Coupling constants (J) are reported in Hz. Splitting patterns are designated: s (singlet), d (doublet), t (triplet), q (quartet), bs (broad singlet), m (multiplet) ABq (AB quartet). Carbon-13 nuclear magnetic resonance spectra were recorded at 75.46 MHz using a Nicolet Magnetics Corporation 1280 spectrometer and are reported in δ relative to the central peak of $CDCl_3$ (77.06 ppm). Infrared spectra were recorded using a Perkin-Elmer 1320 infared spectrophotometer and are reported in cm^{-1}. EI and CI (using the gas reported) low resolution mass spectra were

recorded on a Finnegan 4023 mass spectrometer. High resolution mass spectra were recorded using a Kratos model MS-50 spectrometer.

1-(2-Propenyl)-8-(phenylthio) bicyclo [3.3.1] nonan-3-one **45**

To a solution of bridgehead bromide **40** (0.75 g, 2.33 mmol) and allyltrimethylsilane (1.11 mL, 6.99 mmol) in 4.70 mL of dry methylene chloride at 0 °C, was added silver (I) triflate (0.66 g, 2.56 mmol). The suspension was slowly warmed to ambient temperature while stirring for 10 h. The suspension was diluted with 10 mL of brine, extract twice with 15 mL of methylene chloride and dried over Na_2SO_4. The solution was concentrated *in vacuo* and purified by flash chromatography eluting with 4 : 1 H : EA to afford 0.62 g (91%) of **45**. TLC (4 : 1 H ; EA) R_f = 0.27. ^{1}H NMR δ 1.40 - 1.95 (m, 7 H), 2.08 (d, J = 17.6 Hz, 1 H), 2.21 (dd, J = 13.7 Hz, 7.8 Hz, 1 H), 2.33 - 2.55 (m, 3 H), 2.65 (bd, J = 17 Hz, 1 H), 3.03 (dd, J = 11.4 Hz, 4.7 Hz, 1 H), 5.10 - 5.20 (m, 2 H), 5.75 - 5.93 (m, 1 H), 7.20 - 7.30 (m, 3 H), 7.35 - 7.48 (m, 2 H). ^{13}C NMR δ 28.21, 30.04, 32.17, 38.07, 41.31, 45.21, 46.13, 47.88, 55.90, 119.28, 126.92, 128.81, 132.47, 132.93, 134.88, 211.50. IR ($CHCl_3$) 3080, 3010, 2930, 2860, 1705, 1640, 1585, 1440, 1230, 925, 690 cm^{-1}. Low resolution mass spectrum m/e 55, 67, 79, 91, 109, 119, 135, 150, 177, 245, 286.

Methyl 4-carboxylate-1-(2-propenyl)-8-(phenylthio)-
bicyclo [3.3.1] nonan3-one **47**

To pentane washed KH (0.20 g, 5.0 mmol) at 0 °C, was added dropwise a solution of **45** (0.60 g, 2.09 mmol) in 7.5 mL of dry dimethylcarbonate. The suspension was warmed to ambient temperature and stirred for 16 h. Excess saturated NH_4Cl was added

cautiously to quench the reaction. The mixture was extracted thrice with 25 mL of Et_2O, washed with 25 mL of brine and dried over Na_2SO_4. The crude product was purified by flash chromatography eluting with 3 : 1 H : EA to yield 0.58 g (81%) of **47**. TLC (4 : 1 H ; EA) $R_f = 0.63$. ^1H NMR δ 1.36 - 1.46 (m, 1 H), 1.50 - 1.82 (m, 3 H), 2.10 - 2.23 (m, 2 H), 2.45 (dd, J = 13.7 Hz, 7.8 Hz, 1 H), 2.59 (d, J = 19.8 Hz, 1 H), 2.90 (apparent q, J = 3 Hz, 1 H), 2.97 (dd, J = 14.7 Hz, 4.8 Hz, 1 H), 5.05 - 5.15 (m, 2 H), 5.70 - 5.90 (m, 1 H), 7.20 - 7.30 (m, 3 H), 7.35 - 7.48 (m, 2 H). ^{13}C NMR δ 28.19, 30.06, 32.30, 38.00, 41.38, 46.73, 47.92, 55.90, 57.90, 102.65, 119.30, 127.04, 128.90, 132.60, 132.23, 133.23, 148.06, 172.35, 199.36. IR ($CHCl_3$) 3080, 3010, 2930, 2860, 1705, 1640, 1585, 1440, 1230, 925, 690 cm^{-1}. Low resolution mass spectrum m/e 55, 67, 91, 107, 119, 133, 159, 177, 302.

1-(2-Propenyl)-8-(benzenesulfenyl) bicyclo [3.3.1] nonan-3-one **52**

To a solution of **45** (150 mg, 0.52 mmol) in a 6 : 1 mixture of methanol and water (23 mL) at 0 °C, was added sodium periodate (235 mg, 1.10 mmol) and sodium bicarbonate (49 mg, 0.58 mmol). The suspension was warmed to ambient temperature and stirred for two days. The suspension was diluted with 24 mL of water, extracted thrice with 20 mL of Et_2O, and dried over Na_2SO_4. The crude material was purified by flash chromatography eluting with 1 : 6 H : EA to yield 137 mg (87%) of **52** which was a mixture of diastereomers. TLC (1 : 6 H : EA) $R_f = 0.43$. ^1H NMR δ 0.80 - 1.20 (m, 2 H), 1.42 - 1.56 (m, 1 H), 1.60 - 1.95 (m, 3 H), 2.16 (d, J = 16.5 Hz, 1 H), 2.25 - 2.55 (m, 3 H), 2.79 (dd, J = 14.0 Hz, 8.8 Hz, 1 H), 2.99 (dt, J = 16.5 Hz, 2.1 Hz, 1 H), 3.19 (bd, J = 16.5 Hz, 1 H), , 5.18 - 5.44 (m, 2 H), 5.83 - 6.10 (m, 1 H), 7.40 - 7.80 (m, 5 H). IR ($CdCl_3$) 3010, 2860, 2400, 1705, 1440, 1220, 1185, 1040, 930, 770 cm^{-1}. Low

resolution mass spectrum m/e 55, 67, 79, 91, 107, 119, 135, 159, 177, 245, 285, 302. High resolution mass spectrum requires 302.13405, found 302.13333.

Methyl 4-carboxylate-1-(2-propenyl)-8-(benzenesulfenyl)-bicyclo [3.3.1] nonan3-one **53**

To pentane washed KH (87 mg, 0.76 mmol) at 0 °C, was added dropwise a solution of **52** (100 mg, 0.33 mmol) in 1.2 mL of dry dimethylcarbonate and 1.2 mL of dry THF. The suspension was warmed to ambient temperature and stirred for 16 h. Excess saturated NH_4Cl was added cautiously to quench the reaction. The mixture was extracted thrice with 210 mL of Et_2O, washed with 10 mL of brine and dried over Na_2SO_4. The crude product was purified by flash chromatography eluting with 3 : 2 H : EA to yield 110 mg (92%) of **53**. TLC (3 : 2 H ; EA) $R_f = 0.31$. ^1H NMR δ 0.80 - 1.10 (m, 2H) 1.20 - 1.38 (m, 2 H), 1.64 - 1.75 (m, 2 H), 1.85 - 2.02 (m, 1 H), 2.02 - 2.49 (m, 3 H), 2.73 - 2.98 (m, 3 H), 3.18 - 3.41 (m, 1 H), 5.18 - 5.42 (m, 2 H), 5.82 - 6.08 (m, 1 H), 7.42 - 7.60 (m, 5 H). IR ($CHCl_3$) 3090, 3980, 2790, 1730, 1692, 1640, 1452, 1392, 1280, 910, 700 cm^{-1}. Low resolution mass spectrum m/e 69, 83, 98, 111, 123, 151, 195, 223, 271, 313, 326, 343.

REFERENCES

1. Bohlman, F.; Zedro, C. *Chem. Ber.* **1979**, *112*, 427.
2. Bohlman, F.; Zedro, C. *Chem. Ber.* **1979**, *112*, 435.
3. Bohlman, F.; Surita, A.; Jukupovic, J.; King, R. M.; Robinson, H. *Phytochemistry* **1981**, *20*, 1649.
4. Bohlman, F.; King, R. M.; Robinson, H. *Phytochemistry* **1983**, *22*, 1201.
5. Singh, P.; Jakupovic, J.; Bohlman, F. *Phytochemistry* **1985**, *24*, 1525.
6. Zedro, C.; Bohlman, F.; King, R. M.; Robinson, H. *Phytochemistry* **1986**, *25*, 2873.
7. Zedro, C.; Bohlman, F.; Solomon, J.; Dominguez, X. *Phytochemistry* **1988**, *27*, 849.
8. Ohta, Y.; Hirose, Y. *Chemistry Lett.* **1972**, 263.
9. Gutsche, J. R.; Maycock, E. T. *Tetrahedron* **1968**, *24*, 859.
10. Paquette, L .A. *Top. Curr. Chem.* **1984**, *119*, 1.
11. Cheney, D. L.; Paquette, L. A. *J. Org. Chem.* **1989**, *54*, 334.
12. Danishefsky, S.; Vaughnn, K.; Gadwood, R.; Tsuzki, K. *J. Am. Chem. Soc.* **1981**, *103*, 4136.
13. Fort, R. C., Jr. *Carbonium Ions*; Olah, G.A.; Schleyer, P.V.R., Eds.; Wiley: New York, 1973, Vol IV, Chapter 32.
14. Kraus, G. A.; Hon. Y. -S.; Thomas, P. J.; Laramay, S., Liras, S.; Hanson, J. *Chem. Rev.* **1989**, *89*, 1591.
15. Gray, G. W.; Kelly, S. M. *J. Chem. Soc., PerkinsTrans. II* **1981**, 26.
16. Kraus, G. A.; Hon, Y. -S. *J. Org. Chem.* **1985**, *50*, 4605.

17. Kraus, G. A.; Hon, Y. S. *J. Am. Chem. Soc.* **1985**, *107*, 4341.

18. Kraus, G.A.; Hon, Y.S. *Heterocycles* **1987**, *25*, 377.

19. Heathcock, C. H.; Kleiman, E. F.; Binkley, E. S. *J. Am. Chem. Soc.* **1982**, *104*, 1054.

20. Becker, H. -D.; Mikol, G. L.; Russell, G. A. *J. Am. Chem. Soc.* **1963**, *85*, 3410.

21. Kraus, G. A.; Hon, Y. -S.; Sy, J. *J. Org. Chem.* **1986**, *51*, 2625.

22. Kraus, G. A.; Hon, Y. -S.; Sy, J. *J. Org. Chem.* **1988**, *53*, 1397.

23. Johnson, C. R.; McCants, D., Jr. *J. Am. Chem. Soc.* **1965**, *88*, 2532.

24. Neckers, D. C. *Mechanistic Organic Photochemistry*; Reinhold: New York, 1967, pp 53 - 71.

25. Corey, E. J.; Danheiser, R. L.; Chandrase, K. S.; Siret, P.; Keck, G. E.; Gras, J. -L. *J. Am. Chem. Soc.* **1978**, *100*, 8031.

OVERALL SUMMARY

Part I of this manuscript described a variety of approaches to kaurene natural products. Even though the final goal was not achieved, much information was gained in this study. A tetracyclic intermediate was constructed, but the angular methyl group could not be attached. Two tricyclic intermediates were prepared. In one example an appropriate appendage could not be added that would have allowed the construct of the fourth ring. The other example contained the necessary carbons to achieve the synthesis of kaurene, but the fourth ring could not be realized from this intermediate.

Part II contained an approach to kaurene natural products that was also not successful. This approach was based on a Michael addition followed by an oxy-ene reaction. The precursor to the oxy-ene reaction could not be prepared. The strategy was then changed and based on the cyclization of a bicyclic intermediate to a tricyclic intermediate. This intermediate would contain the necessary functionality to construct the bicyclo [3.2.1] octane moiety found in this class of natural products. A variety of cyclizations were attempted, but the tricyclic precursor was not prepared.

Part III describes an approach to trixiingolide. This project is only in the infant stages, but the route to an advanced intermediate is described. One question yet to be answered is the regioselective aldol condensation.

ACKNOWLEDGEMENTS

I would like to thank Dr. George A. Kraus for his steadfast guidance and support. His continual enthusiasm made my tenure at Iowa State University an enjoyable one.

I would especially like to thank my wife, Mary, who has made my life very gratifying and rewarding. Her continual love and support since I have known her meant a lot to me. I would also like to thank the rest of my family, my parents, my brothers and my sister. Their love and support encouraged me to continue my education.

I would like to thank the members of the Kraus group (the hetero cycle gang) I have worked with over the course of my stay. There were too many to mention individually, but they created a great environment to work in, and they made the many hours spent in lab a little shorter. There are three coworkers that deserve mention: P.J. Thomas, John Walling, and Jeff Thruston. P.J. and John took me under their wing when I began my tenure, and I gained a bit of their knowledge of experimental chemistry. Without their help, I would not be the chemist I am today. I would also like to thank Jeff and the rest of my friends at Iowa State for increasing the quality of my other life. They knew how to blow off steam when it needed to be blown.