

CANADIAN THESES ON MICROFICHE

THÈSES CANADIENNES SUR MICROFICHE



National Library of Canada
Collections Development Branch

Canadian Theses on
Microfiche Service

Ottawa, Canada
K1A 0N4

Bibliothèque nationale du Canada
Direction du développement des collections

Service des thèses canadiennes
sur microfiche

NOTICE

The quality of this microfiche is heavily dependent upon the quality of the original thesis submitted for microfilming. Every effort has been made to ensure the highest quality of reproduction possible.

If pages are missing, contact the university which granted the degree.

Some pages may have indistinct print especially if the original pages were typed with a poor typewriter ribbon or if the university sent us an inferior photocopy.

Previously copyrighted materials (journal articles, published tests, etc.) are not filmed.

Reproduction in full or in part of this film is governed by the Canadian Copyright Act, R.S.C. 1970, c. C-30. Please read the authorization forms which accompany this thesis.

**THIS DISSERTATION
HAS BEEN MICROFILMED
EXACTLY AS RECEIVED**

AVIS

La qualité de cette microfiche dépend grandement de la qualité de la thèse soumise au microfilmage. Nous avons tout fait pour assurer une qualité supérieure de reproduction.

S'il manque des pages, veuillez communiquer avec l'université qui a conféré le grade.

La qualité d'impression de certaines pages peut laisser à désirer, surtout si les pages originales ont été dactylographiées à l'aide d'un ruban usé ou si l'université nous a fait parvenir une photocopie de qualité inférieure.

Les documents qui font déjà l'objet d'un droit d'auteur (articles de revue, examens publiés, etc.) ne sont pas microfilmés.

La reproduction, même partielle, de ce microfilm est soumise à la Loi canadienne sur le droit d'auteur, SRC 1970, c. C-30. Veuillez prendre connaissance des formules d'autorisation qui accompagnent cette thèse.

**LA THÈSE A ÉTÉ
MICROFILMÉE TELLE QUE
NOUS L'AVONS REÇUE**



National Library of Canada

Bibliothèque nationale du Canada

CANADIAN THESES ON MICROFICHE

THÈSES CANADIENNES SUR MICROFICHE

0-315-20284-X

68191

NAME OF AUTHOR/NOM DE L'AUTEUR William H. Romines, III

TITLE OF THESIS/TITRE DE LA THÈSE An Investigation of Alternate Syntheses of Lineatin

UNIVERSITY/UNIVERSITÉ Simon Fraser University

DEGREE FOR WHICH THESIS WAS PRESENTED/ GRADE POUR LEQUEL CETTE THÈSE FUT PRÉSENTÉE M.Sc.

YEAR THIS DEGREE CONFERRED/ANNÉE D'OBTENTION DE CE GRADE 1984

NAME OF SUPERVISOR/NOM DU DIRECTEUR DE THÈSE A.C. Oehlschlager, Professor

Permission is hereby granted to the NATIONAL LIBRARY OF CANADA to microfilm this thesis and to lend or sell copies of the film.

L'autorisation est, par la présente, accordée à la BIBLIOTHÈQUE NATIONALE DU CANADA de microfilmer cette thèse et de prêter ou de vendre des exemplaires du film.

The author reserves other publication rights, and neither the thesis nor extensive extracts from it may be printed or otherwise reproduced without the author's written permission.

L'auteur se réserve les autres droits de publication; ni la thèse ni de longs extraits de celle-ci ne doivent être imprimés ou autrement reproduits sans l'autorisation écrite de l'auteur.

DATED/DATÉ May 27 1984 SIGNED/SIGNÉ _____

PERMANENT ADDRESS/RÉSIDENCE FIXÉ _____

AN INVESTIGATION OF ALTERNATE SYNTHESSES OF LINEATIN

by

William H. Romines, III

B.Sc., Simon Fraser University, 1978

A THESIS SUBMITTED IN PARTIAL FULFILLMENT
OF THE REQUIREMENTS FOR THE DEGREE OF

MASTER OF SCIENCE

in the Department

of

Chemistry

© William H. Romines, III 1984

SIMON FRASER UNIVERSITY

May, 1984

All rights reserved. This thesis may not be reproduced in whole or in part, by photocopy or other means, without permission of the author.

PARTIAL COPYRIGHT LICENSE

I hereby grant to Simon Fraser University the right to lend my thesis, project or extended essay (the title of which is shown below) to users of the Simon Fraser University Library, and to make partial or single copies only for such users or in response to a request from the library of any other university, or other educational institution, on its own behalf or for one of its users. I further agree that permission for multiple copying of this work for scholarly purposes may be granted by me or the Dean of Graduate Studies. It is understood that copying or publication of this work for financial gain shall not be allowed without my written permission.

Title of Thesis/Project/Extended Essay

An Investigation of Alternate Syntheses of Lineatin

Author: WILLIAM H. ROMINES III
(signature)

William H. Romines, III
(name)

May 27, 1984
(date)

ii
APPROVAL

Name: William H. Romines, III

Degree: Master of Science

Title of Thesis: An Investigation of Alternate Syntheses of Lineatin

Examining Committee:

Chairperson: T.N. Bell, Professor

A.C. Oehlschlager, Senior Supervisor

K.N. Slessor

R.K. Pomeroy

E. Kiehlmann, Associate Professor, Department of
Chemistry, Internal Examiner

Date Approved:

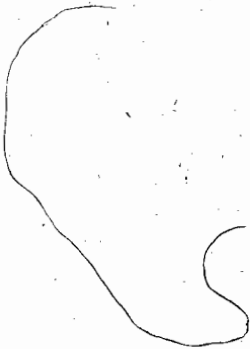
May 22 1984

ABSTRACT

Lineatin, an aggregation pheromone of Trypodendron lineatum, has been shown by previous investigators to be 3,3,7-trimethyl-2,9-dioxatricyclo-[3.3.1.0^{4,7}]nonane and has potential significance as a pest control agent. This thesis is concerned with attempts directed toward developing a facile, high yield synthesis of this pheromone. Two basic approaches were undertaken, both predicated on formation of the cyclobutyl moiety of lineatin.

One approach involved a photochemically mediated (2+2) cycloaddition to construct the four-membered ring. An intramolecular cycloaddition of an appropriately substituted precursor using either photosensitization or catalysis by cuprous salts was unsuccessful. Attempts to circumvent this problem by use of a ketene equivalent in an intermolecular cycloaddition were defeated by an inability to achieve elaboration to give the required cyclobutanol intermediate.

The other approach invoked the use of a sulfur-mediated cyclopropylcarbinyl to cyclobutanone ring expansion. An undesired side-reaction of an appropriately functionalized intermediate precluded execution of the desired ring-expansion. Modification of the substitution pattern of the cyclopropyl intermediate failed to have any effect toward achieving the required ring-expansion. No further attempts were made to synthesize lineatin, as other investigators have recently completed efficient syntheses of the pheromone. These two syntheses as well as the work of previous investigators are also briefly described.



To my father, William H. Romines, Jr.

v

"... there ain't no Coupe de Ville hiding
at the bottom of a Cracker Jack box ..."

- J. Steinman

ACKNOWLEDGEMENTS

I would like to express my appreciation to Ms. M. Tracey for providing the 400 MHz spectra, to Mr. G. Owen for providing the mass spectra and to Dr. A.C. Oehlschlager for his energetic supervision.

A special debt of gratitude is owed to Ms. L. Vincent for the preparation and proofreading of the manuscript in addition to her encouragement and perseverance and to Mr. B.D. Johnston for sharing his technical and academic knowledge as well as his moral support and encouragement and, most especially, for his invaluable friendship.

TABLE OF CONTENTS

	<u>Page</u>
APPROVAL	ii
ABSTRACT	iii
DEDICATION	iv
QUOTATION	v
ACKNOWLEDGEMENT	vi
TABLE OF CONTENTS	vii
INTRODUCTION	1
RESULTS AND DISCUSSION	16
EXPERIMENTAL	36
Preparation of 2,2,4-trimethyl-6-methoxy-5,6-dihydro-2H-pyran (<u>3</u>)	37
Preparation of 2,2,4-trimethyl-6-(3-chloroethoxy)-5,6-dihydro-2H-pyran (<u>4</u>)	38
Preparation of 2,2,4-trimethyl-6-(2'-ene)ethoxy-5,6-dihydro-2H-pyran (<u>5</u>)	39
Attempted intramolecular cyclization of <u>5</u> to lineatin (<u>1</u>)	39
Preparation of 7,7-dibromobicyclo[4.1.0]heptane (<u>6</u>)	40
Preparation of <u>endo</u> - and <u>exo</u> -7-bromo-7-thiomethylbicyclo[4.1.0]heptanes (<u>7</u>)	41
Preparation of <u>endo</u> - and <u>exo</u> -7-carbomethoxy-7-thiomethylbicyclo[4.1.0]heptanes (<u>8a</u> and <u>8b</u>)	42
Preparation of <u>endo</u> - and <u>exo</u> -7-hydroxymethyl-7-thiomethylbicyclo[4.1.0]heptanes (<u>9a</u> and <u>9b</u>)	43

TABLE OF CONTENTS

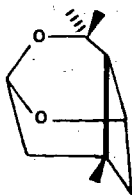
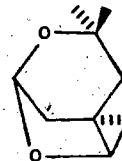
	<u>Page</u>
APPROVAL	ii
ABSTRACT	iii
DEDICATION	iv
QUOTATION	v
ACKNOWLEDGEMENT	vi
TABLE OF CONTENTS	vii
INTRODUCTION	1
RESULTS AND DISCUSSION	16
EXPERIMENTAL	36
Preparation of 2,2,4-trimethyl-6-methoxy-5,6-dihydro-2H-pyran (<u>3</u>)	37
Preparation of 2,2,4-trimethyl-6-(3-chloroethoxy)-5,6-dihydro-2H-pyran (<u>4</u>)	38
Preparation of 2,2,4-trimethyl-6-(2'-ene)ethoxy-5,6-dihydro-2H-pyran (<u>5</u>)	39
Attempted intramolecular cyclization of <u>5</u> to lineatin (<u>1</u>)	39
Preparation of 7,7-dibromobicyclo[4.1.0]heptane (<u>6</u>)	40
Preparation of <u>endo</u> - and <u>exo</u> -7-bromo-7-thiomethylbicyclo[4.1.0]heptanes (<u>7</u>)	41
Preparation of <u>endo</u> - and <u>exo</u> -7-carbomethoxy-7-thiomethylbicyclo[4.1.0]heptanes (<u>8a</u> and <u>8b</u>)	42
Preparation of <u>endo</u> - and <u>exo</u> -7-hydroxymethyl-7-thiomethylbicyclo[4.1.0]heptanes (<u>9a</u> and <u>9b</u>)	43

	<u>Page</u>
Preparation of 7-bicyclo[4.2.0]octanone (<u>10</u>)	45
Preparation of 7,7-dibromo-1-methylbicyclo[4.1.0]heptane (<u>11</u>)	46
Preparation of <u>endo</u> - and <u>exo</u> -7-bromo-7-thiomethyl-1-methyl- bicyclo[4.1.0]heptanes (<u>12</u>)	46
Preparation of <u>endo</u> - and <u>exo</u> -1-methyl-7-carbomethoxy-7-thio- methylbicyclo[4.1.0]heptanes (<u>13</u>)	47
Preparation of <u>endo</u> - and <u>exo</u> -1-methyl-7-hydroxymethyl-7- thiomethylbicyclo[4.1.0]heptanes (<u>14</u>)	47
Preparation of 1-methylbicyclo[4.2.0]octan-7-one (<u>15</u>) and 6-methylbicyclo[4.2.0]octan-7-one (<u>16</u>)	48
Preparation of <u>syn</u> - and <u>anti</u> -2,2,6-trimethyl-4-methoxy-7,7- dibromo-3-oxabicyclo[4.1.0]heptanes (<u>17</u>)	49
Preparation of <u>syn</u> - and <u>anti</u> -2,2,6-trimethyl-4-methoxy-7,7- dichloro-3-oxabicyclo[4.1.0]heptanes (<u>18</u>).	50
Preparation of 2,2,6-trimethyl-4-methoxy-7-chloro-7-thio- methyl-3-oxabicyclo[4.1.0]heptanes (<u>19</u>).	50
Preparation of 2,2,6-trimethyl-4-methoxy-7-carbomethoxy-7- thiomethyl-3-oxabicyclo[4.1.0]heptanes (<u>20</u>).	51
Preparation of 2,2,6-trimethyl-4-methoxy-7-hydroxymethyl-7- thiomethyl-3-oxabicyclo[4.1.0]heptanes (<u>21</u>).	52
Attempted ring expansion of <u>21</u> to fused cyclobutanone: Pre- paration of 3,3,9-trimethyl-5-thiomethyl-2,7-dioxatricyclo- [3.3.1.0 ^{4,5}]nonane (<u>23</u>).	53
Preparation of 2,2,4-trimethyl-5,6-dihydro-2H pyran (<u>24</u>).	53

	<u>Page</u>
Preparation of 2,2,6-trimethyl-7,7-dichloro-3-oxabicyclo- [4.1.0]heptane (<u>25</u>).	54
Preparation of <u>endo</u> - and <u>exo</u> -2,2,6-trimethyl-7-chloro-7- thiomethyl-3-oxabicyclo[4.1.0]heptanes (<u>26</u>).	55
Preparation of 2,2,6-trimethyl-7-carbomethoxy-7-thiomethyl- 3-oxabicyclo[4.1.0]heptane (<u>27</u>).	55
Preparation of 2,2,6-trimethyl-7-hydroxymethyl-7-thio- methyl-3-oxabicyclo[4.1.0]heptane (<u>28</u>).	56
Attempted ring expansion of <u>28</u> to fused cyclobutanone.	57
REFERENCES	58

INTRODUCTION

The ambrosia beetle, Trypodendron lineatum (Olivier), is a major pest to the forest industry throughout the Pacific Northwest and northern Europe. Lineatin, an aggregation pheromone produced by the female of the species, has been shown by laboratory bioassays¹ and field tests² to elicit secondary attraction of these beetles. Initial isolation and identification studies proposed two possible structures for the pheromone³, either 1 or 2. Lineatin was subsequently identified unequivocally as 3,3,7-trimethyl-2;9-dioxatricyclo[3.3.1.0^{4,7}]nonane (1), as a result of unambiguous syntheses^{4,5}. The bioactive enantiomer of the pheromone was

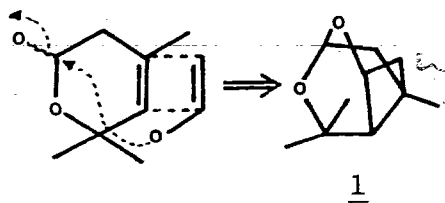
12

demonstrated by field testing to be (+)-lineatin⁶. The absolute configuration of (+)-1 was established to be 1R,4S,5R,7R by a synthesis which provided resolvable chiral intermediates⁷. This assignment of configuration was further confirmed by x-ray crystal structure analysis of another chiral synthetic intermediate⁸.

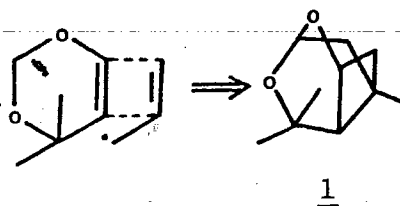
The extensive damage that is inflicted upon fallen and sawn timber by T. lineatum⁹, coupled with the powerful attraction elicited by its pheromone, emphasizes the need for substantial quantities of lineatin for entomological studies. Furthermore, initial field studies indicate that the use of this pheromone for mass trapping will be an effective means of pest

control^{4,6,10}. It is because of this utility as a pest control agent that we have been motivated to develop a facile synthesis of lineatin.

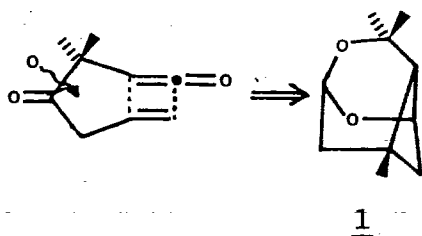
Retrosynthetic analysis of lineatin can best be accomplished by dissecting the molecule between the more highly substituted carbons. Thus, it is easy to visualize a (2+2) cycloaddition proceeding from intermediates of the type I⁴, II¹¹, or III¹². Alternatively, one can, in principle, achieve construction of the lineatin skeleton by means of a Diels-Alder process (type IV)¹¹; via a ring expansion (type V)⁷, or a chain extension-cyclization of a 1,6-anhydrosugar (type VI)¹³. Although the preceding outline does not comprise a complete structural analysis in terms of synthetic derivation, it does serve to illustrate the variety of synthetic approaches possible to envision.



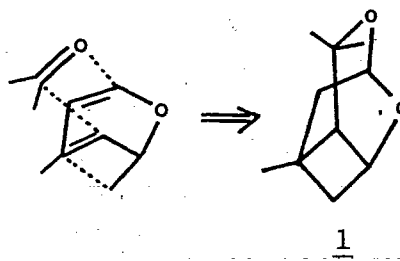
type I



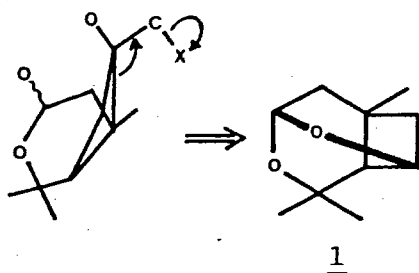
type II



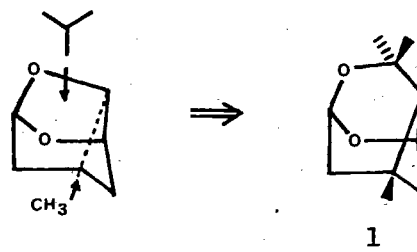
type III



type IV



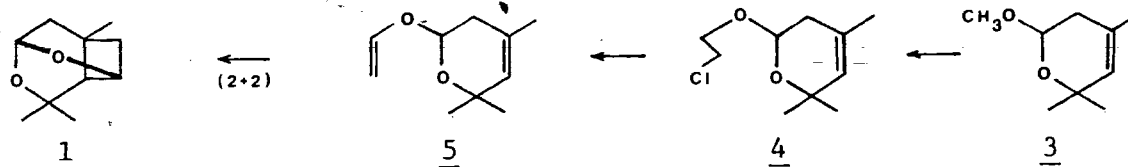
type V



type VI

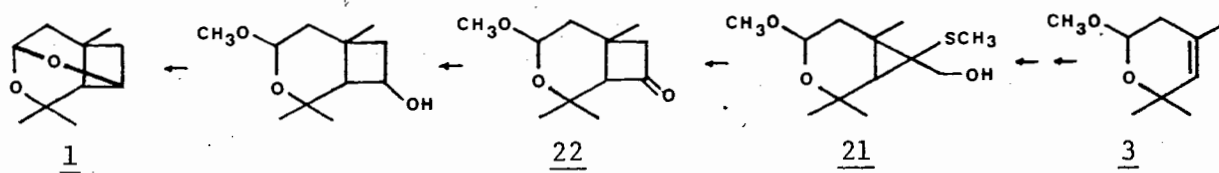
Entomological investigations have demonstrated, not only that (+)-lineatin is the active pheromone, but shown that its enantiomer is benign with respect to eliciting any biological response⁶. Consequently, efforts aimed at large scale syntheses can be directed toward the production of racemic lineatin. Similarly, since the regioisomer, iso-lineatin (2), is neither attractive nor inhibitory, it is not necessary for the purpose of field work applications to have a lineatin preparation entirely free of its 4,5,6 isomer⁶.

Along these lines, this research was aimed at devising and executing a highly efficient synthesis of racemic lineatin. A bias toward a high-yield, large-scale synthesis, as well as consideration of previously reported synthesis work^{4,5,7,8,14}, led us to limiting a proposed synthetic sequence to six or fewer steps. Concommitantly, we concentrated, principally, upon two synthetic approaches, Scheme 1 and Scheme 2.



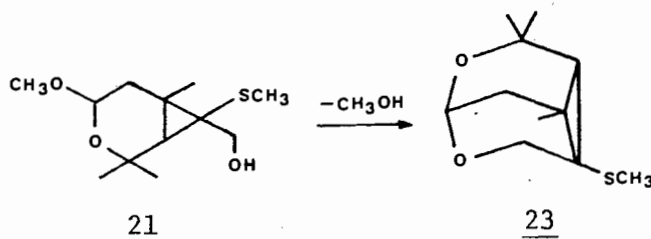
Scheme 1

Scheme 1 was predicated on an intramolecular cross (2+2) photoaddition of the diene 5. All attempts at effecting this transformation proved to be unsuccessful.



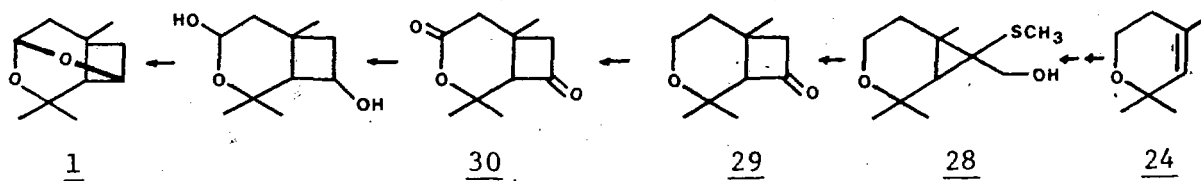
Scheme 2

Scheme 2 utilizes a ring-expansion of the cyclopropylcarbinol 21 to the cyclobutanone 22, based on the work of Trost in synthesizing cyclobutanone¹⁵ and a variety of spirocyclobutanones¹⁶, as well as that reported by Seebach for constructing fused cyclobutanone systems¹⁷. However, attempts to effect this transformation resulted in an acetal-exchange reaction giving the tricyclic acetal 23. We were led to suspect that this reaction resulted from the Meerwein salt, triethyloxoniumtetrafluoroborate, behaving as a Lewis acid thereby catalyzing the elimination of methanol.



Consequently, it was postulated that this competing reaction could be circumvented by employing an intermediate (28) devoid of the sensitive acetal

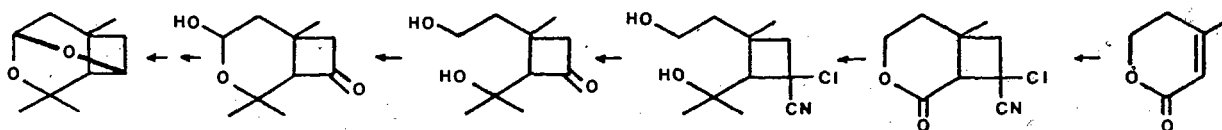
functional group, as depicted for Scheme 2a. This postulated synthetic sequence would invoke the oxidation of an ether to a lactone, a readily achieved transformation using ruthenium tetroxide¹⁸. The starting material (24) for this procedure, as well as the acetal (3), is readily prepared by reduction of 5-hydroxy-3-methyl-3-hexenoic acid lactone. This precursor is particularly attractive as it presents the appropriate oxygen and methyl group substitution pattern and can be readily prepared in large quantities from the BF_3 -catalyzed addition of ketene to mesityloxide¹⁹. This modifi-



Scheme 2a

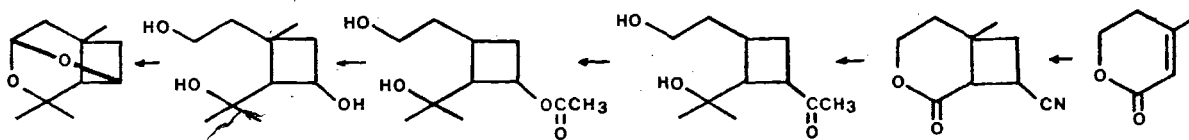
cation to the synthetic procedure, however, also proved to be unsuccessful in achieving the desired ring expansion.

Another synthetic route to lineatin, preemptively investigated, envisioned the use of α -chloroacrylonitrile as a ketene equivalent for a photochemical (2+2) cycloaddition. The use of α -chloroacrylonitrile as the absorbing chromophore, in the presence of acetal 3, merely lead to polymerization²⁰. This problem could be circumvented by using an enone as the UV absorbing chromophore as was done with anhydromevalonolactone in Scheme 3. Despite previous examples where α -chloroacrylonitrile had been used as a ketene equivalent, in Diels-Alder reactions, and, subsequently, converted to a bicyclic ketone^{21,22}, in this instance dehydrohalogenation occurred to give a conjugated nitrile²³. An alternate strategy of employ



Scheme 3

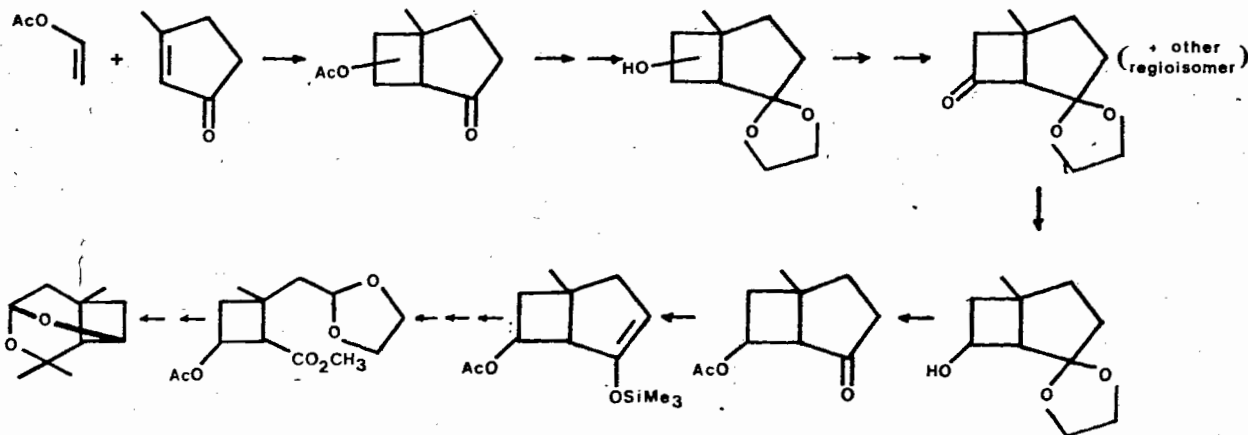
ing acrylonitrile as a substrate for the lactone cycloaddition was summarily dismissed owing to the poor feasibility of elucidating the appropriate oxygenation pattern and the lack of stereospecificity in the proposed Baeyer-Villiger oxidation (Scheme 3a)^{20, 23}.



Scheme 3a

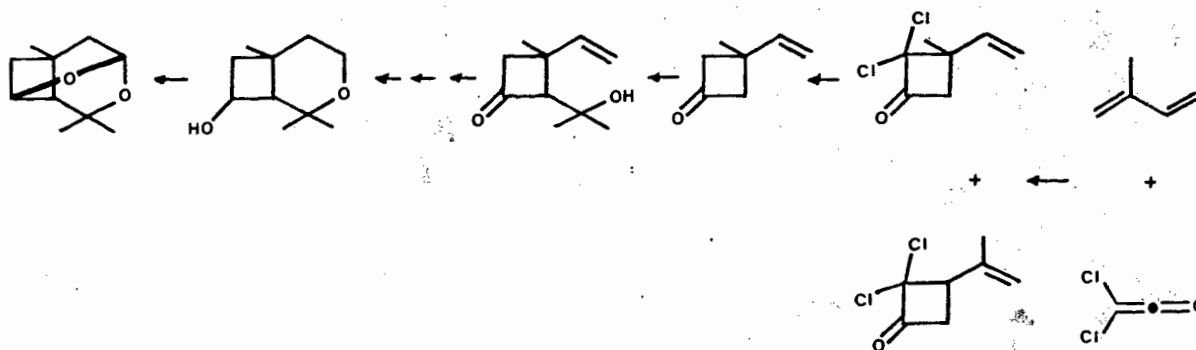
Numerous research groups have intensely investigated the synthesis of lineatin. Approaches invoking a (2+2) cycloaddition via type I predominate in the literature. It was by such an approach that Mori and Sasaki⁵ (Scheme A) constructed the bicyclo [4.2.0] carbon frame of lineatin, employing a photochemically mediated cycloaddition of vinylacetate and 3-methyl-cyclopent-2-en-1-one. One of the prohibitive features of this scheme is that it is necessary to proceed in the reaction sequence from the alcohol state to the carbonyl oxidation state of the cyclobutyl moiety in order to separate the appropriate cyclobutanol regioisomer. Furthermore, the incorrect regioisomer is obtained at this juncture in predominant proportions (4:1). These two considerations, resulting in an overall yield of

0.16% for the twelve-step synthesis, make this route unattractive.



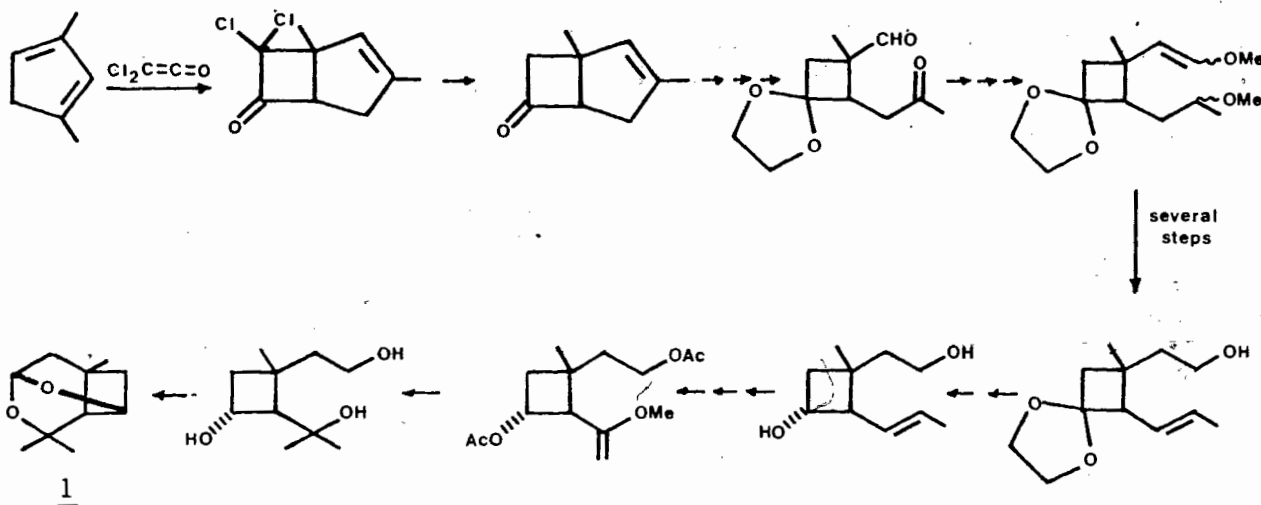
Scheme A

Mori's group subsequently utilized a thermal (2+2) cycloaddition in an alternate synthesis (Scheme B)⁸. The use of dichloroketene and isoprene gave a favourable mixture of isomeric cyclobutanones which, in turn, could be reduced and separated. Alkylation of the appropriate isomer with acetone gave two regioisomers, one of which could be converted to lineatin. Although this nine-step synthesis of 3% overall yield is an improvement over their previous work, it offered no advantage to already existing synthetic methodology. This procedure did, however, provide a crystalline derivative of a resolvable, chiral intermediate which confirmed the previously established absolute configuration of the pheromone.



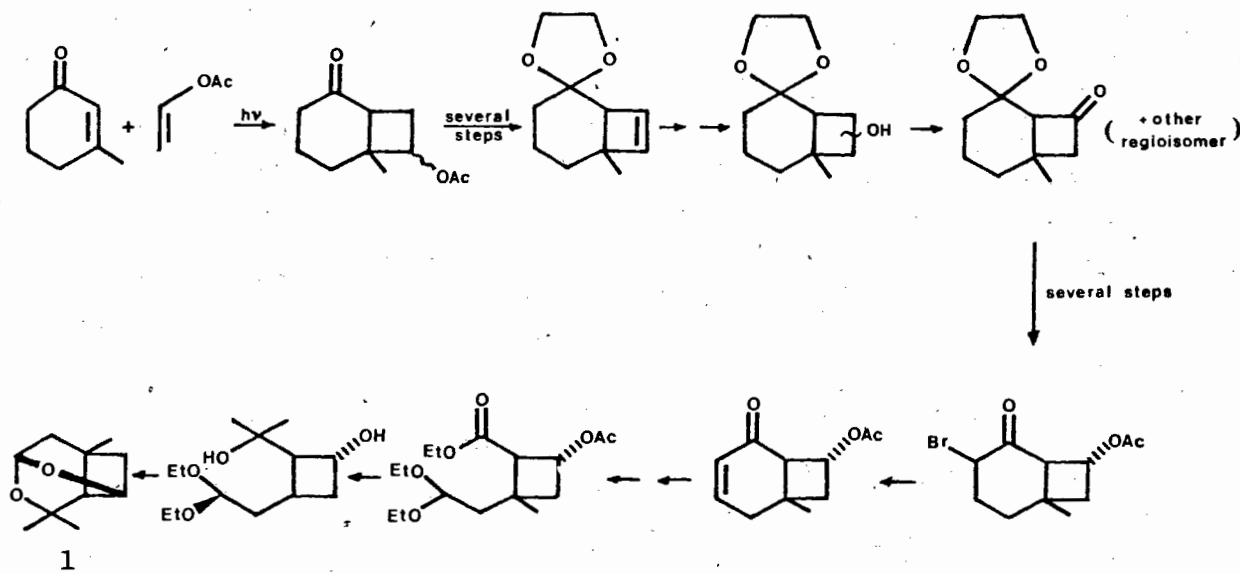
Scheme B

Scheme C was developed by Silverstein and co-workers to provide material for the unambiguous identification of the pheromone⁴. This synthesis also utilizes a (2+2) cycloaddition of type I, commencing with dichloroketene addition to 1,3-dimethyl-1,3-cyclopentadiene. This lengthy eighteen-step sequence which requires extensive manipulation of the oxygenation pattern of the alkyl chains appended to the cyclobutyl ring is both cumbersome and labourious. Though the yields of this process are not reported, the synthesis produced only microgram amounts of the final product and consequently is not an attractive route to lineatin.



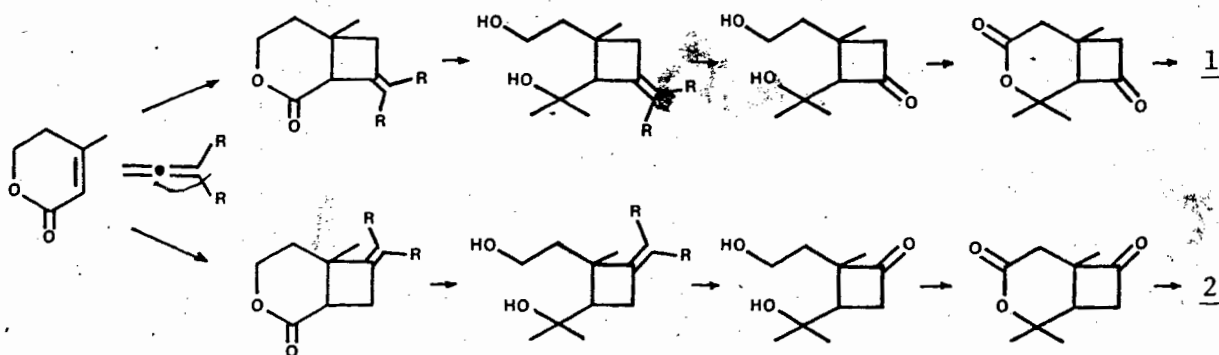
Scheme C

Scheme D, involving yet another (2+2) cycloaddition of type I, was proposed by Silverstein to be a promising mode of synthesis⁴. However, this scheme fails at some point in the elaboration of the appropriate oxygen pattern²⁴ and has never been a source of lineatin.



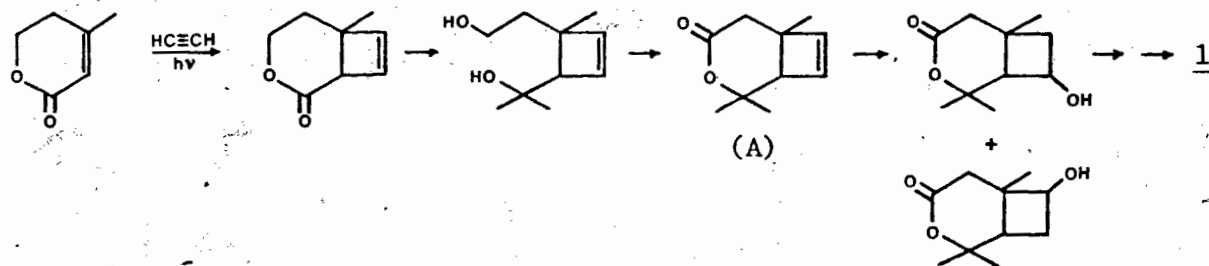
Scheme D

Another route utilizing a (2+2) cycloaddition of type I was advanced by Weiler¹⁴ (Scheme E). In this synthesis, allene and dicyclohexylallene are added photochemically to anhydromevalonolactone. The regioisomers formed in this reaction are obtained in approximately equal amounts and attempts to improve the regioselectivity, either by modifying the substitution pattern of the allene or the conditions of the photolysis, met with failure. The major drawback of this five-step synthesis, which proceeded in 10% overall yield, is the poor regioselectivity in the initial cycloaddition reaction and concomitant difficulty in separation of lineatin (1) from iso-lineatin (2) following completion of the synthesis.



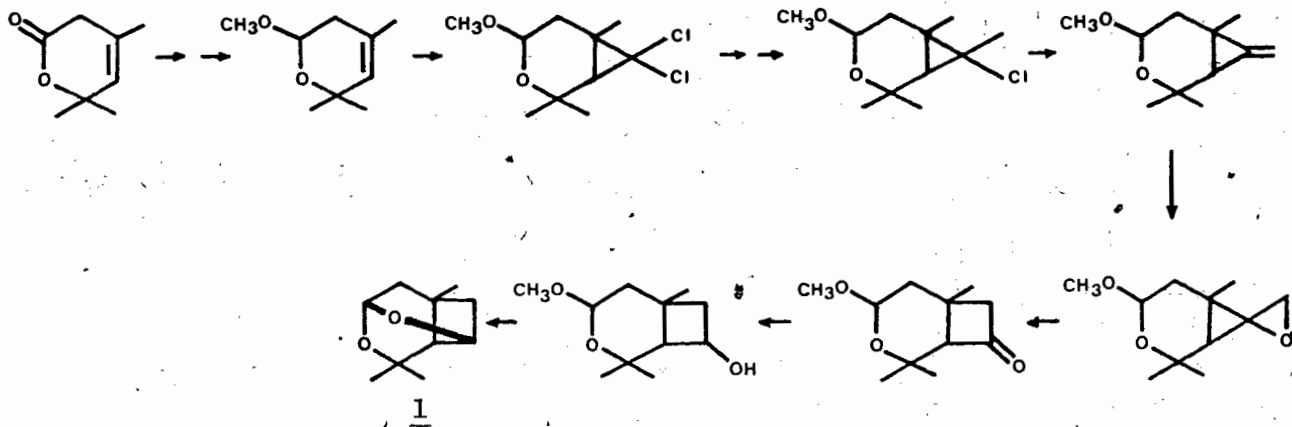
Scheme E

An alternate use of anhydromevalonolactone as a substrate of a photochemical (2+2) cycloaddition was developed by White (Scheme F)²⁵. Acetylene was employed as the cycloaddend in this particular synthesis in the hope of performing a highly regioselective hydroboration of the resultant cyclobutenyl intermediate. The anticipated degree of selectivity of the hydroboration of intermediate A was not achieved, as this olefin was resistant to reaction with hindered dialkyl boranes. Consequently, borane was employed in this reaction to give a mixture of alcohols. The desired regioisomer was readily separated from the mixture upon tosylation and subsequently converted to lineatin. This seven-step synthetic sequence proceeded in a reported 14% overall yield, but produced only a meager 10 mg of product.



Scheme F

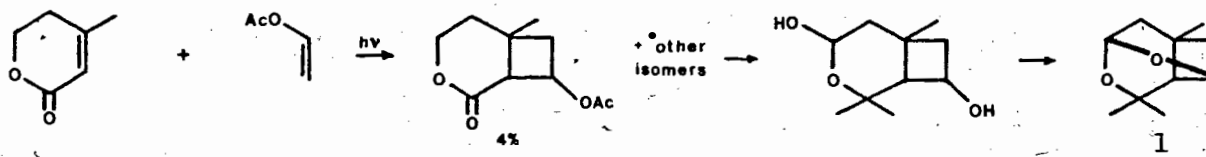
An alternate synthetic strategy employing a ring expansion method, as in type V, led to completion of the first synthesis to supply gram quantities of the pheromone⁷ (Scheme G). This synthesis commences with the attractive synthon, 5-hydroxy-3,5-dimethyl-3-hexenoic acid lactone. Following partial reduction and subsequent methoxylation, the cyclopropyl moiety is introduced by reaction with dichlorocarbene. After converting the dichloro derivatives to the exo-methylene compounds, buffered epoxidation gave the oxaspiropentane isomers which underwent ring expansion according to the method of Aue²⁶ to give a mixture of ketones, wherein the desired regioisomer predominated in a ratio of 4:1. Stereospecific reduction gave the cyclobutanols which were separated by Still's²⁷ rapid chromatography method. Acid-catalyzed cyclization would then be used to produce pure lineatin in 2.8% overall yield, as well as its regioisomer (2).



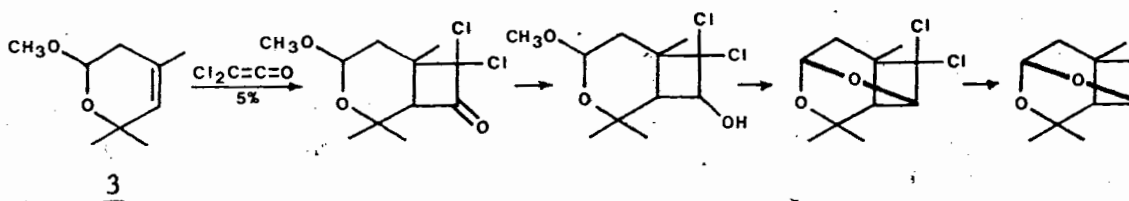
Scheme G

This synthesis was valuable because it supplied gram quantities of lineatin for field testing in 1979⁶. Additionally, resolvable intermediates were provided which allowed the preparation and testing of the optical isomers of the pheromone and established the absolute configuration of the bioactive (+)-lineatin enantiomer. The principle shortcomings of this sequence are the relatively low yield and the need for chromatographic separation of the regioisomeric intermediates obtained from the penultimate reaction.

Scheme H, proposed by Silverstein, and Scheme I, advanced by Slessor, are once again predicated on a type I (2+2) cycloaddition. Both schemes exemplify an apparently efficient, abbreviated sequence of reactions. This efficiency, in terms of the number of steps required in these syntheses, is retarded by the low yield obtained in the initial cycloaddition (4% and 5%, respectively)⁴.



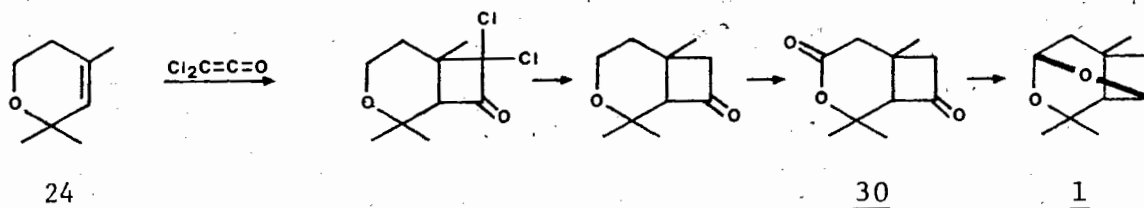
Scheme H



Scheme I

The reasons for the low yield of these cycloaddition reactions are readily attributable. In the case of anhydromevalonolactone with vinylacetate, one would expect the opposite acetate regioisomer to be the predominant product of this photoaddition²⁸. For the addition of dichloroketene to the acetal 3, there are two deleterious effects leading to the poor yield obtained. First, the acetal functionality, present in the product as well as the substrate, is readily susceptible to acid-catalyzed degradation. The method of generation of the dichloroketene, whether it be dichloroacetylchloride and trialkylamine or trichloroacetylchloride and zinc dust, gives rise to formation of acidic by-products, trialkylammonium chloride or zinc dichloride, which are capable of inducing degradation of these acetals. Additionally, dichloroketenes are reported to give notoriously poor yields of cycloadducts with trisubstituted olefins²⁹ and with allylic ethers³⁰. This is due primarily to competing reactions of dichloroketene

polymerization and a type of Claisen rearrangement with allylic ethers leading to dichlorolactones as products. These detracting factors in the use of dichloroketene cycloaddition in an abbreviated sequence of reactions have been overcome in a recently completed synthesis of lineatin³¹ (Scheme J).

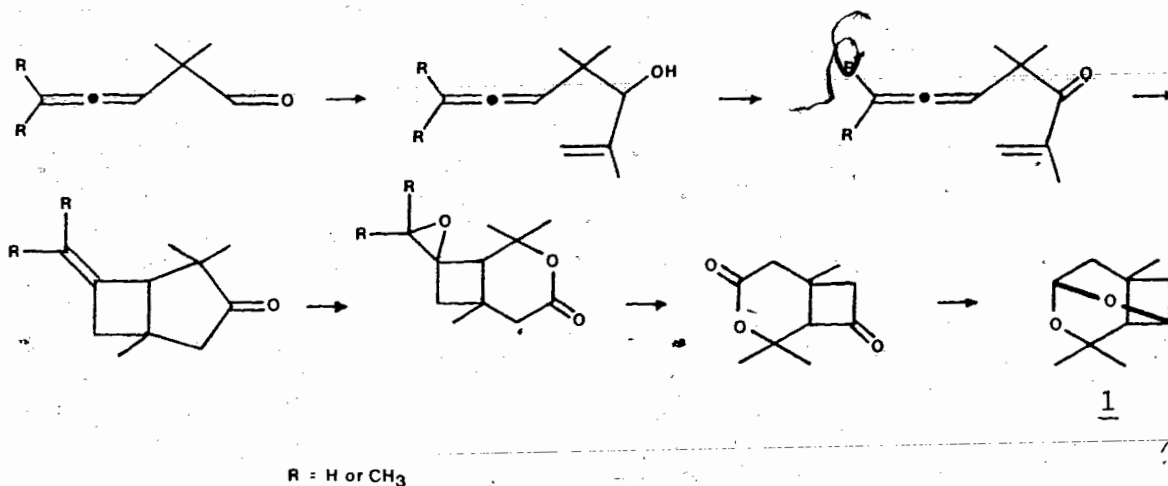


Scheme J

In order to circumvent the problem of acid-catalyzed degradation of the acetal, the ether 24 was employed as an alternate substrate for the cycloaddition. To counteract the competing insertion reaction of dichloroketene with this allylic ether, dimethoxyethane was added to the reaction to complex the zinc chloride formed in the generation of the dihaloketene. The resultant cycloadduct was reduced with zinc dust in ammonium chloride saturated methanol to give the dehalogenated ketone. Conversion of this intermediate to the crystalline lactone proceeds readily by oxidation with ruthenium tetroxide. Subsequent reduction with a hindered hydride reagent, followed by acidic work-up, gives pure lineatin in high yield. This abbreviated, five-step synthesis is completed with a 12% to 15% overall yield and is the only synthesis to date which has been employed to produce the pheromone in large multigram quantities³².

The most recent synthesis of lineatin reported in the literature which rivals this efficiency is one by a Scandinavian group¹² (Scheme K) which

employs a type III cycloaddition strategy. This synthesis is initiated with either of two readily available allenic aldehydes. Alkylation with the Grignard of methallyl chloride followed by a standard oxidation produced the ketone precursor for the thermal (2+2) cycloaddition. After isolation of the desired bicyclic ketone, sequential oxidation with meta-chloroperbenzoic acid then periodic acid gave the familiar ketolactone which is readily converted to lineatin.



Scheme K

This six-step synthesis produces the pheromone in a higher overall yield, 30% to 35%, than any other previously completed procedure. The only major drawback of this sequence is the critically narrow temperature range that must be employed in the cycloaddition. Furthermore, this procedure should be readily adapted to production of optically active lineatin and, in fact, work is in progress to that end. Other investigators are also engaged in the synthesis of enantiomerically pure lineatin³³ utilizing Stork's method of stereospecific cyclobutane formation, as employed in the synthesis of grandisol³⁴.

RESULTS AND DISCUSSION

The diene 5, used as the photochemical substrate in Scheme 1 is readily prepared in a short, high yield sequence from 5-hydroxy-3,5-dimethyl-3-hexenoic acid lactone. The lactone is partially reduced with lithium aluminum hydride and the hemiacetal is methylated with trimethylorthoformate to give the mixed acetal 3. An efficient acetal exchange is achieved with freshly distilled 2-chloroethanol, neutralized over sodium bicarbonate, by acid catalysis and azeotropic removal of the methanol formed. Dehydrohalogenation of the resultant primary chloride (4) is accomplished by treatment with potassium t-butoxide in refluxing t-butanol. Using an amidine base such as 1,6-diazabicyclo[4.3.0]nonane (DBN)³⁵ failed to effect any elimination, whereas use of t-butoxide in dimethylsulfoxide (DMSO)³⁶ proved to be too harsh, resulting in degradation of the organic substrate.

Photochemical activation of the diene 5 was attempted, initially, by employing triplet sensitizers with triplet energies in the approximate range estimated for the molecule's olefinic linkages³⁷: 75-85 kcal/mol range for the endocyclic double bond and circa 80 kcal/mol for the vinyl ether. The envisioned reaction pathway for such a process would most likely involve a diradicaloid intermediate³⁸. As illustrated in Figure 1, formation of intermediate i would be less favoured than intermediate ii, based on the relative stabilities of a primary radical versus a secondary radical which is alpha to an oxygen atom. However, considering the preference of a looser diradicaloid geometry for the triplet stage and due to the favoured formation of a six-membered (as opposed to a seven-membered) ring in the transition state, one would expect intermediate i to be formed

preferentially. Sensitizers which have been employed include acetophenone, xylene, toluene, benzene, and acetone. None was able to elicit ring closure.



Figure 1

Alternatively, singlet sensitization proceeding through a zwitterionic intermediate³⁹ (Figure 2) has been shown to promote (2+2) cycloadditions of vinyl ethers that are unresponsive to triplet sensitization⁴⁰. Attempted sensitization with methyl benzoate resulted in no consumption of the starting material.

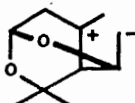


Figure 2

Attention was also directed at charge-transfer reagent catalysis of the desired cycloaddition. This charge-transfer induction of the cycloaddition is based on an electron migration from the electron-rich double bond of the substrate 5 to an electron deficient acceptor molecule to form a radical-ion species. This is accompanied by reverse electron migration, which then proceeds to give product (Figure 3). Thus, electron deficient molecules capable of UV activation can act as electron sinks during

photochemically induced reactions of electron-rich substrates⁴¹. Naphtho-
nitrile, tetracyanoethylene, and trinitrobenzene were employed in an at-
tempt to effect this transformation. None resulted in any significant
consumption of the starting material.

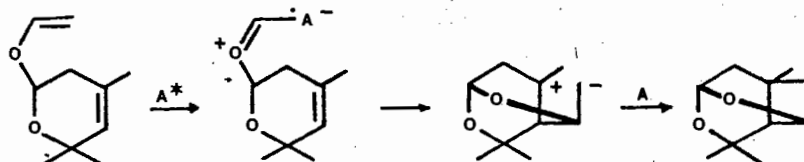


Figure 3

Yet another mode of photochemical activation for promotion of cycloaddition reactions is copper catalysis. Cuprous salts have been reported to induce both cyclodimerization of olefins and (2+2) cycloadditions of dienes⁴². This process, presumably, would involve electron donation from the most nucleophilic double bond, yielding an octet stabilized intermediate which could then be neutralized by attack of the remaining double bond, followed by collapse of the organocopper intermediate⁴³ (Figure 4).

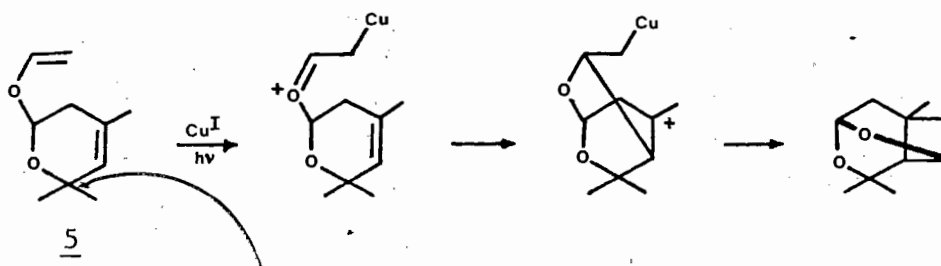


Figure 4

Cuprous chloride and bistriphenylphosphine cuprous borohydride were tested as catalysts for this photochemical transformation. Both salts were ineffective at promoting any reaction of the diene 5. Copper(I)trifluoromethane sulfonate (copper triflate) is reported to be the preferred catalyst for effecting the intramolecular (2+2) cycloadditions of dienes⁴⁴. Use of copper triflate in the photochemical reaction resulted in no formation of lineatin or the iso-lineatin regioisomer. However, gradual consumption of the diene substrate 5 was detected by GC analysis. This consumption of starting material is attributed to acid-catalyzed degradation of the acetal functionality, owing to trace amounts of trifluoromethane sulfonic acid present in the preparation of copper triflate⁴⁵. In an effort to circumvent the problem of acid-catalyzed side reactions, copper(II)bistrifluoromethane sulfonate (copper ditriflate) was used as a photochemical activator. Copper ditriflate is readily prepared free of any traces of acid after recrystallization⁴⁶. Furthermore, copper ditriflate is reported to undergo in situ photochemical reduction to the active copper(I) species to promote (2+2) cycloadditions⁴⁷. However, irradiation of the pheromone precursor 5 in the presence of copper ditriflate failed to achieve any ring closure. At this point, photochemically mediated closure of 5 as an approach to the synthesis of lineatin was abandoned.

An alternate strategy of employing a photochemical (2+2) cycloaddition is the use of a ketene equivalent in an intermolecular reaction. An attractive ketene equivalent for utilization in a synthesis of lineatin is α -chloroacrylonitrile owing to the polarity about the olefinic bond. This distinct polarity provides an effective means of manipulating the regiochemical course of an intermolecular cycloaddition. Thus, one can envision

α -chloroacrylonitrile participating either as the UV absorbing chromophore (Figure 5) or as the ground state olefin (Figure 6) in a photochemical cycloaddition to yield an appropriately functionalized, fused cyclobutyl system. This regioselectivity of reaction is predicated on the reversal of ground state bond polarities in the photoexcited state⁴⁸. Unfortunately, when α -chloroacrylonitrile is employed as the absorbing chromophore in the presence of acetal 3 it leads to autopolymerization, exclusively.

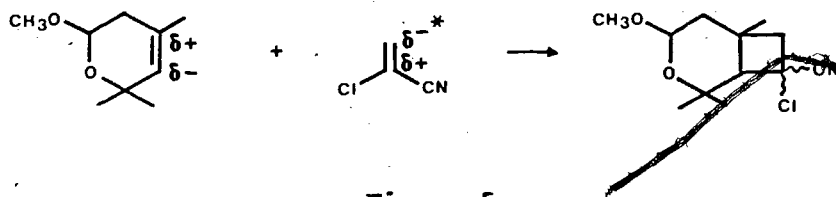


Figure 5

Therefore, it was decided to employ α -chloroacrylonitrile as the ground state olefin in a photochemical cycloaddition with anhydromevalonolactone (Figure 6). This reaction, in fact, proceeded smoothly in acetonitrile to give the desired pair of regioisomers in high yield²³. It was anticipated that an abbreviated sequence of reactions to give lineatin from this cycloadduct could be readily achieved (see Scheme 3). This synthetic methodology was subsequently dismissed as attempted conversion of the α -chloronitrile to a bicyclic ketone resulted in dehydrohalogenation.

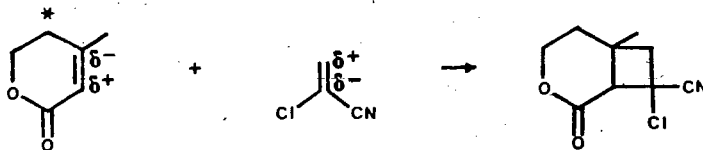


Figure 6

Previous investigators utilized α -chloroacrylonitrile as a ketene equivalent dienophile in Diels-Alder reactions and successfully converted the α -chloronitrile to a ketone via basic hydrolysis^{21,22}. It had been postulated, in the case of sodium sulfide in ethanol²² and, by inference, for alcoholic hydroxide, that the reaction proceeded via a displacement mechanism. Recent evidence, however, demonstrates that, when hydroxide is employed as the base, attack occurs at the nitrile carbon and the resultant α -chloroamide, in turn, undergoes base hydrolysis to the ketone⁴⁹ (Figure 7). Consequently, cyclobutyl adducts derived from α -chloroacrylonitrile are much more susceptible to an E-2 process resulting in dehydrohalogenation, rather than a nucleophilic attack resulting in an α -chloroamide degradation which must proceed through a highly strained spiro-lactam type intermediate (such as iii or iv). This is in contrast to the readily achieved conversion of α -chloronitriles to ketones observed for cyclohexyl adducts.

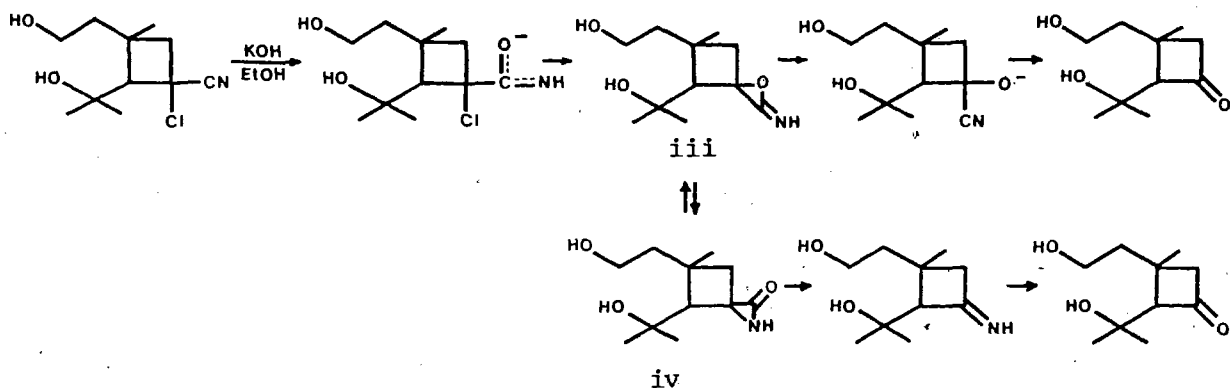


Figure 7

Acrylonitrile was also considered as an alternate ground state olefin for a photochemically induced condensation with anhydromevalanolactone

(Scheme 3a). It is well known that methyllithium, in addition to alkylation of carbonyl compounds, converts nitriles to methyl ketones⁵⁰. The resulting methyl ketone from such a series of reactions could be readily converted, by means of Baeyer-Villiger oxidation⁵¹, to an acetate which, after hydrolysis, would give a cyclobutanol. However, despite the predicted regiospecificity of photochemical reaction, the stereoselectivity is poor giving a mixture of endo and exo nitrile isomers. This would result in an equally undesired mixture of cyclobutanol stereoisomers. As only the endo cyclobutanol would cyclize to give lineatin, this synthetic strategy would require extensive manipulation via further oxidations and reductions to efficiently place the hydroxyl in the required stereochemical position.

The other principal approach toward the synthesis of lineatin investigated utilized a ring-expansion to construct the cyclobutyl ring. The ring-expansion methodology employed was the cyclopropyl carbinol to cyclobutanone conversion. The preferred procedure for effecting this transformation employs an α -sulfenyl cyclopropylcarbinol¹⁵⁻¹⁷. Previous investigators had successfully constructed 2,2-disubstituted¹⁶ and 2,3,4-trisubstituted cyclobutanones¹⁷ by this procedure. For our purposes, a 2,3-disubstituted cyclobutanone is required as an intermediate. As it was anticipated that the acetal 3 would be an ideal starting material for such a synthetic sequence, it was necessary to develop an effective procedure for conversion of a cyclic olefin to an appropriately functionalized, fused cyclopropylcarbinol (Figure 8). This synthetic methodology, including ring expansion to a fused cyclobutanone, was initially explored with the model compounds, cyclohexene and 1-methylcyclohexene, employed as starting materials.

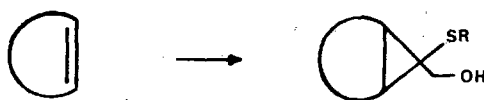


Figure 8

Two approaches were explored for construction of the required α -sulfenyl cyclopropylcarbinol intermediate. The first approach involves cyclopropanation of the alkene substrate with the carbenoid derived from ethyl diazoacetate (EDA). Enolization of the resulting cyclopropyl ester and reaction of the enolate with a disulfide to give an α -sulfenyl ester, followed by hydride reduction, would give the desired cyclopropyl precursor. This particular strategy encountered two obstacles that prevented its execution.

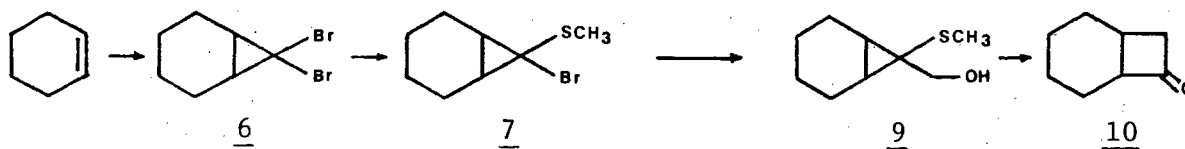
First, although copper(II)acetoacetate catalyzed cyclopropanation of the model substrates with EDA proceeded smoothly in high yield with an exo-endo ratio of stereoisomers as reported in previous procedures⁵², all attempts at sulfenylating the resultant cyclopropyl ester failed. Cyclopropyl hydrogens are more acidic than other alkyl hydrogens owing to a greater s character of their molecular orbital, whereas protons α to an ester carbonyl owe their enhanced acidity to a stabilizing enolate resonance structure requiring greater p orbital character. Therefore, these two acidity-enhancing effects need not be complimentary. In fact, it was initially postulated that the counteractivity of these contributions prohibited formation of the requisite carbanion⁵³. Recent evidence, however, suggests that the desired anion is formed by treatment of a cyclopropyl ester with lithium diisopropylamide (LDA). However, this anion is

extremely reactive when formed and leads to products derived from a Claisen condensation⁵⁴. This most probably arises due to the sluggish ionization of the cyclopropyl carboxylate and, in fact, there are several instances in which formation of a cyclopropyl ester anion is precluded⁵⁵. Other investigators have tried to circumvent this difficulty by employing the dianion of the free cyclopropyl acid and have enjoyed a modicum of success. But, trimethylsilyl chloride appears to be the only electrophile to successfully be alkylated by this dianion: use of alkyl halides and carbonyl compounds resulted, principally, in recovery of starting materials⁵⁶. Furthermore, the lineatin precursor 3 was inert toward cyclopropanation by EDA. Cyclopropanations of olefins by EDA are initiated either by photochemical activation⁵⁷ or by homogeneous catalysis. Two mechanisms of this alkene cyclopropanation are operative⁵⁸. In the case of catalysis by palladium, the reaction proceeds through a complexation of the olefin, whereas with rhodium catalysis, as with photochemical activation, a free carbene species is involved. Catalysis of the reaction by copper seems to proceed through an intermediate mechanism. As palladium catalysis is inoperative for trisubstituted olefins⁵⁹, rhodium would appear to be the catalyst of choice for cyclopropanation of the acetal 3. However, reaction of the olefin 3 with EDA, using either rhodium acetate or copper acetoacetate as a catalyst, or irradiation, lead merely to formation of diethyl maleate and diethyl fumarate and recovery of the unreacted alkene substrate.

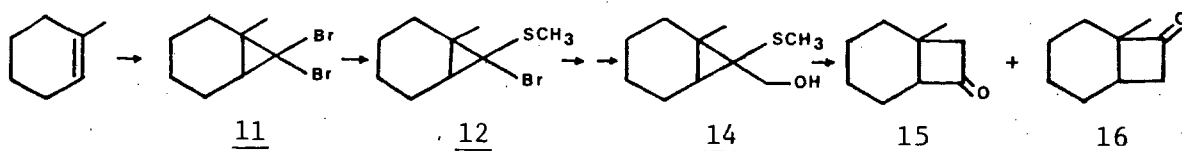
Consequently, attention was directed toward an alternate approach for constructing the desired cyclopropylcarbinol intermediates. This approach also employs a carbenoid cyclopropanation of an olefin. Use of a chloro-thio carbene equivalent followed by a metal-halogen exchange reaction

and capture of the resultant carbanion with a formaldehyde equivalent would give the desired α -sulfenyl cyclopropylcarbinol. Although chloromethylthio carbene has been used to cyclopropanate alkenes, the yields of such reactions have been only poor to moderate, even with relatively simple alkenes⁶⁰, and would seem to offer little synthetic utility in the application to lineatin synthesis. Therefore, it was decided to proceed by dihalocarbene cyclopropanation followed by sequential lithium-halogen exchange reactions to perform sulfenylation and carbonylation reactions, respectively.

This methodology was successful for the conversion of cyclohexene and 1-methylcyclohexene to the desired fused cyclobutanones (Scheme 2b and Scheme 2c). So it was that each alkene was converted to the respective bicyclic geminal dibromides, 6 and 11, by standard phase-transfer catalyzed⁶¹ generation of dibromo carbene from bromoform and hydroxide. Low-temperature lithium-halogen exchange lead to the desired α -bromo sulfides 7 and 12 upon trapping of the α -lithiobromide at -95° with dimethyldisulfide. A second lithium-halogen exchange reaction was performed and the resultant stabilized carbanion was carbonylated at ambient temperature with carbon dioxide to give the respective carboxylate salts. Acidification, then esterification with diazomethane, gave the methyl esters which were purified by distillation. Lithium aluminum hydride reduction of the carboxyl residue proceeded smoothly to give the requisite α -sulfenyl cyclopropylcarbinols 9 and 14.

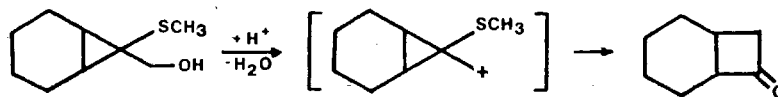


Scheme 2b



Scheme 2c

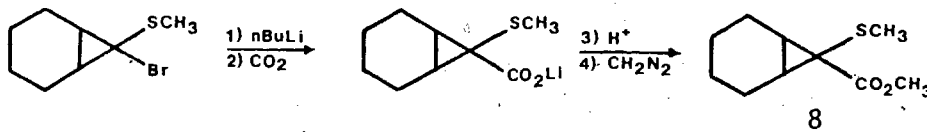
A variety of acid-catalyzed conditions have been employed for effecting ring expansion of analogous cyclopropylcarbinols such as para-toluene-sulfonic acid^{16,17}, stannic chloride^{16b}, and hydrofluoroboric acid^{16b}, reputedly the method of choice⁶². However, under these reaction conditions, the starting materials 9 and 14 were recovered unchanged, even after prolonged reaction times. This lack of reactivity could presumably be due to the difficulty of forming the initial primary carbonium intermediate (Equation 1).



Equation 1

Consequently, an alternate methodology had to be employed. Alkylation of the sulfur with trialkyloxonium tetrafluoroborate followed by treatment with hydroxide lead directly to formation of the desired fused cyclobutanones. This approach had also been successfully employed by Trost in analogous systems^{16b}, and it is postulated that the reaction proceeds via an oxaspiropentane intermediate based on previous studies whereby an open chain α -sulfenylcarbinol is converted to the corresponding epoxide⁶³.

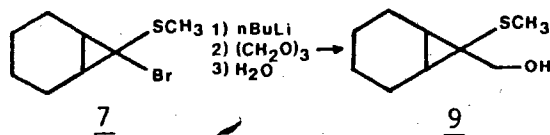
In this manner, cyclohexene was converted to the bicyclic ketone 10 and 1-methyl cyclohexene to the corresponding bicyclic ketone regioisomers 15 and 16 (in a ratio of approximately 3 to 1) in overall yields of 34% and 29%, respectively. The yields of all the reactions in this sequence were satisfactory except for the carbonylation of the α -lithiosulfide intermediate (Equation 2). It was decided to further investigate this transformation with the hope of improving the moderate yield.



Equation 2

It was found that performing the sequential lithiations as a one-pot reaction leading directly from the dibromide 6 to the ester 8 without isolation of the intermediate bromosulfide had no appreciable effect on the overall yield for this transformation. Use of the formaldehyde trimer, trioxane, to give the alcohol 9 directly from alkylation with the α -lithiosulfide (Equation 3), proceeded in a lower yield than the carboxylation.

sequence. Therefore, it was presumed that para-formaldehyde would offer no enhancement of the yield in this transformation.



Equation 3

The most successful method found for conversion of the bromosulfide to the hydroxy sulfide was a transcarbonylation reaction with dimethylformamide (DMF)⁶⁴. In a one-pot reaction the dibromide 6 is converted to the α -lithiosulfide which is subsequently reacted with DMF to give, after aqueous work-up, the corresponding aldehyde. The aldehyde, without purification, was reduced with sodium borohydride to give the alcohol in 69% yield for the multistep process (Equation 4).

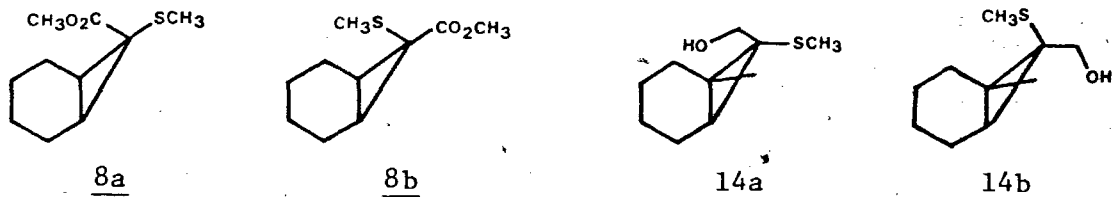


Equation 4

The modification allowed for a 30% enhancement in the overall yield for the conversion of cyclohexene to 7-bicyclo[4.2.0]octanone. Furthermore, this sequence employs only reactions that are performed under either basic or neutral conditions. The avoidance of acidic conditions is desirable for the application of this methodology to the synthesis of lineatin (Scheme 2) where the starting material 3 contains the acid-sensitive acetal

functional group. The prerequisite for employing neutral or basic conditions is, fortunately, also met in the selection of the mode of ring-expansion employed for the synthesis of the model compounds.

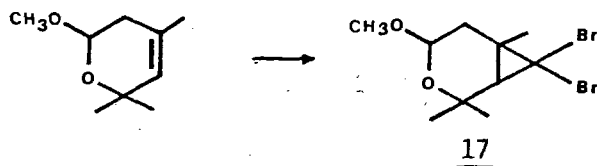
Although it is not necessary for synthetic purposes to separate the endo and exo stereoisomers of the various intermediates, analytical samples of the stereoisomeric α -thio esters 8a and 8b and the α -thio carbinols 14a and 14b were obtained to confirm that the predominant stereoisomers are the exo-sulfides 8a and 14a. This assumption is based on the fact that the kinetically favoured exo-lithium species is formed preferentially in the initial lithium-halogen exchange reaction⁶⁵. This would lead to formation of predominantly the endo-lithium stereoisomer upon lithiation of the α -bromosulfide intermediate and, should isomerization of the carbanion species occur, it would be more likely to happen at this stage with warmer temperatures and longer reaction times to give preferentially the endo-lithium, exo-sulfide⁶⁶.



That 8a is the predominant ester stereoisomer was corroborated by comparison of the ¹³C NMR and the chemical shift assignments of C-7 for the respective stereoisomers. The assignment of structures is based on the greater steric compression at C-7 for the endo ester 8a resulting in a higher field resonance⁶⁷ relative to that for 8b (32.5 ppm as compared to 36.6 ppm). A ¹H NMR experiment confirmed the structure of the predominant

alcohol stereoisomer as being 14a. Reciprocal enhancement of the NMR signals was observed upon irradiation of the C-6 hydrogen and the hydrogens of the thiomethyl group in an NOE⁶⁸ experiment for the major isomer 14a but not 14b. This confirmed the structure of 14a as the exo-sulfide.

In the adaptation of this ring-expansion methodology for the synthesis of lineatin, it was initially decided to prepare the dibromo derivatives 17 (Equation 5). Its formation, however, proved to be sluggish and failed to go to completion after 7 days at room temperature even with the use of a large excess of bromoform and hydroxide. Consequently, it was decided to employ the dichloro derivative 18 instead. This known compound is readily prepared in high yield utilizing essentially the same reaction conditions to generate dichlorocarbene rather than dibromocarbene (see Scheme 2). Additionally, it was felt that the resultant α -chlorosulfide would be more stable than the corresponding bromo compounds and that the lithium-halide exchange reaction of 18 would encounter less difficulty than that for 17.



Equation 5

The temperature dependence of the lithiation of the dichloride 18 proved to be quite critical. It is well known that at temperatures above -90° α -lithiochloride species undergo thermal decomposition to the corresponding carbenes, via elimination of the halide, resulting in allene⁶⁹ and carbene insertion products⁷. When the temperature of this specific

lithiation is maintained below -95° no reaction occurs and the substrate is recovered unreacted. This lack of reactivity is, presumably, due to the decreased solubility of the dichloride at these low temperatures, resulting in the substrate precipitating from the solution. By carefully maintaining the reaction temperature in the narrow range between -95° and -90° , the lithiation proceeds smoothly and the resultant carbanion is successfully trapped with dimethyldisulfide to give the desired α -chlorosulfide 19 in high yield.

Use of DMF as a substrate for alkylation by the α -lithiosulfide intermediate in the subsequent reaction proved to be unsuccessful. The failure of the carbonyl carbon of DMF to be alkylated in this reaction was attributed to steric effects. It appeared that only two of a possible four stereoisomers were formed in the previous and subsequent reactions, those being the two exo-sulfides. This would entail that in the initial lithium-halogen exchange reaction the kinetically-favoured exo-lithium species is formed exclusively as one would expect owing to the stringent temperature conditions imposed on the reaction and the greater steric hindrance of the endo-chloride in 18 relative to the model compounds. Consequently, when the sulfides 19 undergo the lithium-halogen exchange only the sterically encumbered endo-carbanion is formed. This species is likely further stabilized by intramolecular coordination of the lithium with one or both oxygens of the acetal functionality (Figure 9)⁷⁰. The steric encumbrance about the carbanionic centre coupled with the steric hindrance afforded by the geminal dimethyl moiety of DMF probably precluded the condensation of the reactants.

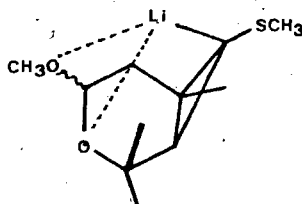
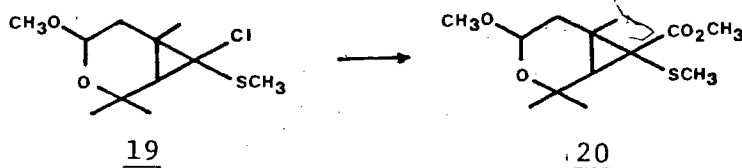


Figure 9

In an effort to circumvent this problem, it was decided to revert to the use of carbon dioxide as the carbonylating reagent for this reaction. After termination of the reaction by dilution with water, the carboxylate salt was protonated by addition of a stoichiometrically deficient amount of aqueous acid. The organic acid was immediately extracted with dichloromethane and esterified with diazomethane. This sequence of protonation, extraction and esterification was repeated several times until no further carboxylate product could be isolated. By this means the desired ester was obtained in a moderate yield without any appreciable degree of acid-catalyzed degradation of the acetal moiety (Equation 6).



Equation 6

Lithium aluminum hydride reduction of the ester proceeded readily to give the desired cyclopropylcarbinol 21 in excellent yield. Treatment of the stereoisomeric alcohols with Meerwein salt, however, lead directly to

formation of the tricyclic acetal, 23. Variation in the reaction conditions had no effect on altering the course of the reaction. Evidently, the trialkyloxonium tetrafluoroborate serves as a Lewis acid to catalyze the elimination of methanol to form the observed product. This postulation is advanced on the basis that precautions were taken to ensure that no traces of protic acid were present in the solution and that alkylation at sulfur would be preferred owing to the presumed greater nucleophilicity of sulfur relative to oxygen⁷¹ and, further, that an hydroxyl oxygen would be more nucleophilic than an ether oxygen. This elimination of methanol to give the tricyclic acetal 23 is virtually a quantitative reaction: all the starting material is consumed and only a single product is observed. This further substantiates the argument proposed earlier, that only the exo-sulfide stereoisomers are formed in the course of this synthetic sequence. Were there any endo-sulfide present in the reaction it would either undergo a competing reaction or be recovered unchanged as it would be incapable of cyclizing to the product (Figure 10).

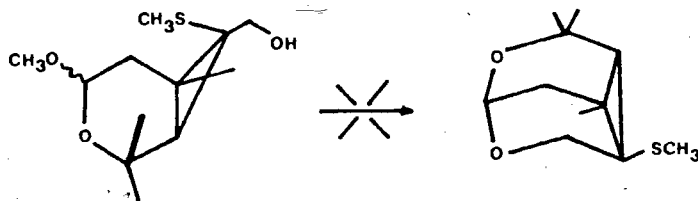
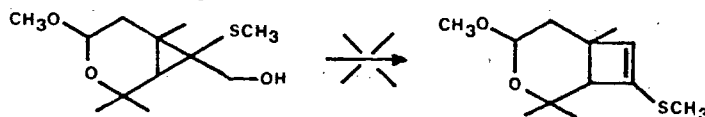


Figure 10

Other methods of alkylation were attempted including dimethylsulfate and methyl iodide, either thermally or with silver ion catalysis. None was able to effect the desired reaction. Alternatively, α -thiocyclopropyl

carbinols can be converted to thiocyclobutenes^{16b} which, in turn, can be hydrolyzed to the corresponding cyclobutanones. This reaction was explored employing the Burgess' salt (carboxylsulfamoyl)triethylammonium hydroxide inner salt methyl ester⁷², to effect the desired transformation. This procedure lead merely to degradation of the starting material giving a complex mixture of products (Equation 7).



Equation 7

Although the thiocyclobutene 31 was tentatively identified as one of the many minor products of the reaction and this compound could conceivably be transformed to lineatin, the abominable yield and chemoselectivity attained make this transformation nonviable for our synthetic purpose. Instead, attention was directed to Scheme 2a.



31

It was hoped that by use of the ether 24, rather than the acetal 3, the problem of the side reaction encountered when attempting the ring-expansion to the cyclobutanone could be avoided. Furthermore, oxidation of the bicyclic ketone to the desired lactone would not be expected to present any difficulty and this particular keto-lactone 30, as well as the

keto-acetal 22, are readily reduced and cyclized to the pheromone, as observed in other syntheses.

The cyclopropylcarbinol 28 was prepared employing virtually the same reaction conditions as for 21 without difficulty and in a slightly improved yield. Once again, attempted ring-expansion failed to produce any of the desired bicyclic ketone. Treatment of 28 with trialkyloxonium tetrafluoroborate provided a myriad of products, none of which constituted more than 10% of the mixture.

Our inability to effect the desired ring-expansion of the appropriate synthetic intermediates was in agreement with other investigators who found that satisfactory yields could not be obtained in all cases^{16b,73}, even after substantial experimentation employing a wide variety of reaction conditions. No further efforts toward the synthesis of lineatin were undertaken as other investigators have recently achieved high yield, efficient syntheses of this pheromone⁷⁴ (Scheme J³¹ and Scheme K¹²).

EXPERIMENTAL

NMR spectra were recorded on Varian Associates EM-360 and XL-100 and Bruker WM400 spectrometers. Chemical shifts are reported in δ units, parts per million (ppm) downfield from tetramethylsilane. Splitting patterns are described as s, singlet; d, doublet; t, triplet; q, quartet; and m, multiplet. Coupling constants are reported in Hertz (Hz). Unit resolution mass spectra were obtained by using a Hewlett-Packard 5985B GC/MS/DS system operating at 70 eV. High resolution mass spectra were provided by Dr. G. Eigendorf, at the University of British Columbia, using a Kratos DS-50 mass spectrometer. Elemental analyses were performed by Mr. M. Yang, of the Department of Biological Sciences, Simon Fraser University, using a Perkin-Elmer Model 240 elemental analyzer. Infra-red (IR) spectra were recorded as neat films on a Perkin-Elmer 599B grating spectrometer.

Analytical gas chromatography (GC) was performed on a Hewlett-Packard 5830A, using a 0.25 mm i.d. \times 30 m SP-1000 capillary column programmed to change the column temperature from 100° to 180° at 8°/min (column A), or on a Hewlett-Packard 5880A gas chromatograph, using either a 0.21 mm i.d. \times 30 m SP-2100 capillary column (column B) or a 0.24 mm i.d. \times 15 m DB-1 capillary column (column C) programmed from 100° to 250° at 10°/min. Preparative gas chromatography was performed on a Varian Aerograph Model 1700, using either a 1/4 in. i.d. \times 6 ft. carbowax column (column D) maintained at 180° or a 1/4 in. i.d. \times 5 ft. SP-1000 column (column E) maintained at 120°.

Thin layer chromatography (TLC), 0.25 mm, and preparative TLC, 20 cm \times 20 cm \times 0.75 mm, plates were prepared from silica gel 60 GF₂₅₄. All column chromatography was performed using Kieselgel 60 (40-63 μ m), as described by

Still²⁷. Solvents employed for chromatography, hexane (hex), ethyl acetate (EtOAc), methylene chloride and ether, were distilled prior to use. Compositions of solvent mixtures are reported as volume ratios.

All reactions requiring anhydrous conditions were conducted using glassware that had been flame-dried under a flow of dry argon. Tetrahydrofuran (THF) was distilled from lithium aluminum hydride, N,N-dimethylformamide (DMF) and dimethyldisulfide were distilled from calcium hydride, and methylene chloride was distilled from phosphorus pentoxide immediately prior to use. Ether and hexane were dried and stored over sodium wire.

Diazomethane was prepared from N-methyl-N-nitrosotoluene-4-sulfonamide, following the recipe provided on the label of Aldrich's Diazald[®] and performed on such a scale so as to ensure a minimum of a ten per cent excess when employed.

Preparation of 2,2,4-trimethyl-6-methoxy-5,6-dihydro-2H-pyran (3).

A solution of 56 gm (0.4 mol) of 5-hydroxy-3,5-dimethyl-3-hexenoic acid lactone in 80 mL of dry THF containing 25 mL of ether was cooled to -30° by means of a dry ice-acetone bath. To this mixture was added 4.55 gm (0.12 mol) of LiAlH_4 in 140 mL of THF over a period of 15 min. The solution was allowed to warm to r.t. and was stirred for an additional 30 min. The reaction was terminated by pouring the mixture into 300 gm of ice containing 12 mL of conc. H_2SO_4 . The ether layer was withdrawn and the aqueous portion was extracted with ether (2×150 mL). The combined ether extracts were washed with 75 mL of 5% NaHCO_3 and 75 mL of saturated NaCl , dried over anhyd. MgSO_4 , filtered, and concentrated in vacuo.

Without further purification, this concentrated reaction mixture was reacted with 40 mL of trimethylorthoformate and 1.5 gm of ammonium nitrate

in 15 mL of methanol. The reaction was stirred 14 hr at r.t and 5 hr at reflux. The mixture was poured into 120 mL of water and extracted with methylene chloride (3 × 75 mL). The combined organic extracts were washed with 90 mL of saturated NaCl, dried over anhyd. MgSO₄, filtered, and concentrated by distillation at atmospheric pressure. Distillation under vacuum gave 42.3 gm (68%), b.p. 62-66°, 15 mm Hg (lit.⁷ b.p. 62-67°, 15 mm Hg); ¹H NMR (60 MHz, CDCl₃) δ 5.28 (1H, C=CH, s), 4.70 (1H, O-CH-O, t, J=5 Hz), 3.41 (3H, OCH₃, s), 2.05 (2H, CH₂, d, J=5 Hz), 1.67 (3H, C=C-CH₃, s), 1.27 (3H, CH₃, s), 1.23 (3H, CH₃, s).

Preparation of 2,2,4-trimethyl-6-(3-chloroethoxy)-5,6-dihydro-2H-pyran (4).

A mixture of 25.7 gm (0.35 mol) of 2-chloroethanol and 14.2 gm (0.1 mol) of 3 was dissolved in 350 mL of benzene. A catalytic amount (≈10 mg) of para-toluenesulfonic acid was added and the solution was stirred at r.t. for 30 min. Approximately one-half of the solvent was removed, in vacuo, and ≈150 mL of benzene was added to the solution which was then stirred for an additional 30-40 min. This sequence of steps was repeated. The reaction was terminated by passing the solution over a neutral alumina column and washing through with pentane. The resultant solution was dried over anhyd. MgSO₄, filtered, concentrated in vacuo, and distilled to yield 15.9 gm (86%), b.p. 65°, 5 mm Hg; mass spectrum m/e (relative intensity) 206/204(1), 191(29), 189(100), 125(10), 109(28), 96(20), 81(22); ¹H NMR (60 MHz, CDCl₃) δ 5.33 (1H, C=CH, s), 4.92 (1H, CH, t, J=5 Hz), 3.72 (6H, 3CH₂, m), 1.68 (3H, C=C-CH₃, s), 1.28 (3H, CH₃, s), 1.25 (3H, CH₃, s).

Anal. Calcd. for C₁₀H₁₇O₂Cl: C, 58.68; H, 8.37. Found: C, 58.52; H, 8.32.

Preparation of 2,2,4-trimethyl-6-(2'-ene)ethoxy-5,6-dihydro-2H-pyran (5).

Under an inert (N₂) atmosphere, 250 mL of 2-methyl-2-butanol were brought to reflux temperature. 10.1 gm (90 mmol) of potassium tertiary-butoxide was added and the solution was stirred for 30 min prior to the addition of 6.14 gm (30 mmol) of 4. The solution was stirred at reflux for an additional 4 hr. After cooling to r.t., the reaction was diluted with 200 mL of water and extracted with pentane (2 × 250 mL). The combined pentane extracts were washed with water (2 × 150 mL), dried over anhyd. MgSO₄, filtered, and concentrated by distillation at atmospheric pressure. Distillation under vacuum gave 4.37 gm (87%), b.p. 80-82°, 15 mm Hg; mass spectrum m/e (relative intensity) 168(1), 153(2), 125(100), 109(30), 107(66), 97(29), 79(21), 55(32); ¹H NMR (400 MHz, CDCl₃) δ 6.29 (1H, C=CH-O, dd, J=14,6.6 Hz), 5.37 (1H, C=CH, q, J=1.6 Hz), 5.23 (1H, O-CH-O, dd, J=4.4,4.2 Hz), 4.49 (1H, CH₂=C-O, dd, J=14, 1.5 Hz), 4.13 (1H, CH₂=C-O, dd, J=6.6,1.5 Hz), 2.22 (1H, CH₂, dd, J=17.0,4.2 Hz), 2.11 (1H, CH₂, dd, J=17.0,4.4 Hz), 1.72 (3H, C=C-CH₃, d, J=1.6 Hz), 1.28 (3H, CH₃, s), 1.25 (3H, CH₃, s).

Anal. Calcd. for C₁₀H₁₆O₂: C, 71.39; H, 9.59. Found: C, 71.32; H, 9.63.

Attempted intramolecular cyclization of 5 to lineatin (1).

The use of benzophenone as a sensitizer exemplifies the procedure employed to conduct this photochemical reaction. In a quartz vessel, purged with N₂, were deposited 250 mg (1.5 mmol) of 5, 100 mg decane, 96 mg (0.5 mmol) of benzophenone, and 80 mL of hexane. This solution was irradiated for a period of 48 hr using a Hanovia 200-watt mercury-vapour u.v. lamp. Aliquots were periodically withdrawn from the solution, diluted with

several mL of pentane, and analyzed by GC (column A). No consumption of starting material was detected.

Decane was used as an internal standard for GC analysis. A variety of triplet and singlet sensitizers, charge-transfer complexes and metal catalysts were employed in attempts to effect the desired photochemical reactions; these included benzophenone, acetophenone, benzene, benzaldehyde, toluene, xylene, naphthonitrile, methyl benzoate, acetone, tetracyanoethylene, copper(I)bis(triphenylphosphine)borohydride, copper(I)chloride, copper(I)trifluoroethanesulfonate, and copper(II)bis-(trifluoromethanesulfonate). Hexane, benzene ether, and acetonitrile were employed as solvents. Reaction times varied from 22 hr to 60 hr. In no instance was any lineatin or its isomer, iso-lineatin, ever detected by GC analysis. In only two instances were there ever detected any significant consumption (as much as 10%) of the starting material: using acetone as a sensitizer most probably resulting in oxetane formation (tentatively identified by GC-MS) and in the reaction with copper(I)trifluoromethanesulfonate resulting in acid-catalyzed degradation of the acetal, 5, due to the presence of traces of trifluoromethane sulfonic acid.

Preparation of 7,7-dibromobicyclo[4.1.0]heptane (6).

To a solution of 49.2 gm (0.6 mol) of cyclohexene and 176.9 gm (0.7 mol) of bromoform in 50 mL of benzene were added 2 gm (5.5 mmol) of ethyltrimethylammonium bromide and a chilled 50% NaOH solution (250 gm NaOH in 250 mL H₂O). The two-phase reaction mixture was stirred vigorously at r.t. for 26 hr, then diluted with 500 mL of pentane and 1 L of water and filtered through celite. The aqueous layer was extracted with 300 mL of ether. The combined organic extracts were washed with water (2 × 500 mL),

dried over anhyd. MgSO_4 , filtered, and concentrated in vacuo to yield, after distillation, 131.2 gm (86%), b.p. 63-64°, 1.2 mm Hg (lit.^{17b} b.p. 80°, 5 mm Hg) 96% pure by GLC (column A); mass spectrum m/e (relative intensity) 254(4), 256, 252(2), 214(42), 212(81), 210(44), 93(100), 77(49), 68(88).

Preparation of endo- and exo-7-bromo-7-thiomethylbicyclo[4.1.0]heptanes (7).

Under an argon atmosphere, 25.4 gm (100 mmol) of 6, in 300 mL of anhyd. ether, were cooled to -105° (ether/liquid N_2 bath). Over a period of 25 min, 50 mL (120 mmol) of 2.4 M n-butyllithium in hexane were added with the reaction temperature maintained below -100°. The reaction mixture was stirred for a further 45 min at -100° prior to addition of 14 mL (158 mmol) of dry dimethyldisulfide. The reaction was maintained below -90° for 30 min, then gradually allowed to warm to r.t. overnight while remaining under an argon atmosphere. The reaction was terminated upon addition of 400 mL of water and extracted with pentane (2 × 350 mL). The combined pentane extracts were washed with 1 M Na_2CO_3 (2 × 250 mL), dried over anhyd. Na_2SO_3 , filtered, and concentrated in vacuo to yield after distillation 20.5 gm (93%), b.p. 61-66°, 0.2 mm Hg (lit.^{17c} b.p. 77-78°, 1.5 mm Hg); mass spectrum m/e (relative intensity) 222, 220(3), 140(85), 125(65), 93(55), 91(100); ^1H NMR (60 MHz, CDCl_3) δ 2.3 (3H, SCH_3 , s), 1.1-2.0 (10H, 4 CH_2 and 2CH, m).

Preparation of endo- and exo-7-carbomethoxy-7-thiomethylbicyclo[4.1.0]-heptanes (8a and 8b).

Under an argon atmosphere, 50 mL (120 mmol) of 2.4 M n-butyllithium in hexane were added at -5° to a solution of 13.3 gm (60 mmol) of 7 in 250 mL of hexane. The resultant mixture was stirred at 0° for 40 min. The argon flow was then replaced by a flow of CO_2 , and the reaction was subsequently stirred at 0° for 30 min and an additional 3 hr while warming to r.t. The reaction mixture was then combined with 400 mL of 1 M Na_2CO_3 and washed with hexane (2×200 mL). The aqueous layer was acidified to pH ≈ 2 by the addition of conc. HCl and extracted with ether (3×200 mL). The combined ether extracts were dried over anhyd. Na_2SO_3 , filtered, and combined with a freshly prepared ether solution of diazomethane. The resultant solution was dried over anhyd. Na_2SO_4 , filtered, and concentrated in vacuo to yield after distillation 6.9 gm (57%), b.p. $58-63^{\circ}$, 0.2 mm Hg; >95% pure 7.2:1 ratio of 8a and 8b by GC (column A). Preparative GC on column D gave pure 8a and 8b.

For 8a (faster eluting, major isomer): mass spectrum m/e (relative intensity) 200(35), 185(8), 168(38), 125(100), 91(18); ^1H NMR (60 MHz, CDCl_3) δ 3.65 (3H, OCH_3 , s), 2.15 (3H, SCH_3 , s), 1.75-1.07 (10H, $\text{C}_1\text{-C}_6$, m); ^{13}C NMR (100 MHz, CDCl_3) δ 169.6 (C=O), 51.7 (OCH_3), 32.5 (C_7), 24.2 (C_2 and C_5), 20.6 (C_3 and C_4), 20.2 (C_1 and C_6), 15.2 (SCH_3).

For 8b (slower eluting, minor isomer): mass spectrum m/e (relative intensity) 200(24), 185(5), 168(46), 125(100), 91(17); ^1H NMR (60 MHz, CDCl_3) δ 3.68 (3H, OCH_3 , s), 2.13 (3H, SCH_3 , s), 1.94-1.27 (10H, $\text{C}_1\text{-C}_6$, m); ^{13}C NMR (100 MHz, CDCl_3) δ 172.2 (C=O), 52.5 (OCH_3), 36.6 (C_7), 27.3 (C_2 and C_5), 21.1 (C_3 and C_4), 19.1 (C_1 and C_6), 14.5 (SCH_3).

HRMS Calcd. for $C_{10}H_{16}O_2S$: 200.0872. Found: 200.0879.

Preparation of endo- and exo-7-hydroxymethyl-7-thiomethylbicyclo[4.1.0]-heptanes (9a and 9b).

Method A: A solution of 4.4 gm (22 mmol) of 8 in 50 mL of ether was added to a suspension of 4.56 gm (120 mmol) of $LiAlH_4$ in 100 mL of ether at r.t. and the reaction was maintained at reflux for an additional 2 hr. After cooling to r.t., excess hydride was consumed by dropwise addition of ethyl acetate. Following addition of 60 mL of 20% NaOH, then 100 mL of water, the products were extracted with ether (3×100 mL). The combined ether extracts were dried over anhyd. Na_2SO_4 , filtered, and concentrated in vacuo to yield after distillation 3.74 gm (98%), b.p. 77-81°, 0.3 mm Hg; 97% pure 9a and 9b, in a ratio of 7.4:1 (column A).

Method B: Under an argon atmosphere, 34 mL (81 mmol) of 2.4 M n-butyllithium in hexane were added to 8.8 gm (40 mmol) of 7 in 150 mL of hexane at -5°. The resultant mixture was stirred at 0° for 1 hr and an additional hr at r.t. after which time 56 mL (28 mmol) of 0.5 M trioxane in ether was added. As the reaction was exothermic, it was necessary to re-apply the ice bath in order to maintain the reaction temperature below 30°. After stirring at r.t. for 4 hr, the reaction was terminated by addition of 100 mL of saturated NH_4Cl and extracted with ether (2×150 mL). The combined organic extracts were washed with 200 mL of water, then 150 mL of saturated NaCl, dried over anhyd. Na_2SO_4 , filtered, and concentrated in vacuo. The residue was purified by column chromatography on a 5 cm \times 26 cm column of silica gel 60, 230-400 mesh. The column was washed with 800 mL of hexane to remove nonalcohol impurities. The desired products were then eluted with 800 mL of ether to yield 3.0 gm (44%); >95% pure by GC

(column A).

Method C: To 6.35 gm (25 mmol) of 6 in 200 mL of ether were added 12 mL (28.8 mmol) of 2.4 M n-butyllithium in hexane under argon at $\approx -105^\circ$. During the course of this addition and the subsequent 40 min of stirring, the reaction temperature was maintained below -100° . After which time 3.5 mL (≈ 40 mmol) of dimethyldisulfide were added. The reaction was stirred at -100° for 30 min, then allowed to gradually warm to -10° . At this juncture, the ether-nitrogen dewar was replaced with an ice-salt water bath and 25 mL (60 mmol) of 2.4 M n-butyllithium in hexane were added to the reaction mixture. The resultant solution was stirred at -5° for 40 min and an additional 90 min at r.t. 30 mL of DMF was then added. Due to the exothermic reaction, it was necessary to reapply the ice bath during the course of this addition in order to maintain the reaction temperature below 30° . The reaction was left stirring at r.t. for 4 hr, then terminated upon addition of 100 mL of 5% HCl. The layers were separated and the aqueous phase extracted with 200 mL of ether. The combined organic extracts were washed with water (2×200 mL), dried over anhyd. Na_2SO_4 , filtered, and concentrated in vacuo to yield 3.81 gm of crude aldehyde. This residue, employed without further purification, was dissolved in 20 mL of ethanol and added dropwise to a solution of 760 mg (20 mmol) of NaBH_4 in 20 mL of ethanol at -5° . The reaction was stirred at r.t. overnight, then diluted with 100 mL of water, followed by 15 mL of 10% HCl. The aqueous layer was extracted with ether (3×50 mL). The combined ether extracts were washed with 70 mL of water, dried over anhyd. Na_2SO_4 , filtered, concentrated in vacuo, and purified by chromatography (as per Method B) to yield 2.95 gm (69%) of the desired alcohols.

Pure 9a and 9b were obtained by preparative TLC (hexane:ethyl acetate, 3:2, v:v).

For 9a (major component, $R_f = 0.53$): mass spectrum m/e (relative intensity) 172(5), 157(61), 154(18), 141(23), 139(100), 91(46), 79(46); ^1H NMR (400 MHz, CDCl_3) δ 3.69 (2H, CH_2O , d, $J=6$ Hz), 2.29 (1H, OH, t, $J=6$ Hz), 2.07 (3H, SCH_3 , s), 1.93 (2H, CH_2 , m), 1.48 (2H, CH_2 , m), 1.24 (6H, 2 CH_2 and 2CH, m).

For 9b (minor component, $R_f = 0.28$): mass spectrum m/e (relative intensity) 172(7), 157(46), 154(20), 141(26), 139(100), 91(49), 81(42), 79(57), 77(41); ^1H NMR (400 MHz, CDCl_3) δ 3.63 (2H, CH_2OH , m), 2.28 (1H, OH, m), 2.07 (3H, SCH_3 , s), 1.91 (2H, CH_2 , m), 1.59 (2H, CH_2 , m), 1.49 (2H, CH_2 , m), 1.25 (2H, CH_2 , m), 1.10 (2H, 2CH, m).

HRMS Calcd. for $\text{C}_9\text{H}_{16}\text{OS}$: 172.0922. Found: 172.0922.

Preparation of 7-bicyclo[4.2.0]octanone (10).

To 1.38 gm (8 mmol) of 9 and 50 mL of methylene chloride under argon were added 12 mL (12 mmol) of 1.0 M triethyloxonium tetrafluoroborate in methylene chloride. The resultant solution was stirred at r.t. for ≈ 22 hr under an argon atmosphere, then 30 mL (15 mmol) of 0.5 M NaOH were added. After stirring the two-phase reaction an additional 24 hr at r.t., it was combined with 60 mL of water and extracted with 120 mL of pentane. The organic extract was washed with 60 mL of saturated NaCl, dried over anhyd. MgSO_4 , filtered, and concentrated by distillation at atmospheric pressure. Distillation under vacuum gave 734 mg (74%), b.p. 65-68°, 7 mm Hg (lit.⁷⁵ b.p. 62-63°, 5 mm Hg); mass spectrum m/e (relative intensity) 124(16), 82(58), 81(29), 67(100); ^1H NMR (60 MHz, CDCl_3) δ 2.9 (3H, C_6 and C_8 , m), 1.1-1.9 (9H, $\text{C}_1\text{-C}_5$, m).

Preparation of 7,7-dibromo-1-methylbicyclo[4.1.0]heptane (11).

To a solution of 57.7 gm (0.6 mol) of 1-methylcyclohexene and 176.9 gm (0.7 mol) of bromoform in 50 mL of benzene were added 2 gm (5.5 mmol) of cetyltrimethylammonium bromide and a chilled 50% NaOH solution (250 gm NaOH in 250 mL H₂O). The two-phase reaction mixture was stirred vigorously for a period of 24 hr, then diluted with 500 mL of pentane and 1 L of water and filtered through Celite. The aqueous layer was extracted with 300 mL of ether. The combined organic extracts were subsequently washed with water (2 × 500 mL), dried over anhyd. MgSO₄, filtered, and concentrated in vacuo to yield after distillation 141.9 gm (88%), b.p. 83-84°, 1.1 mm Hg; mass spectrum m/e (relative intensity) 268(12), 270, 266(6), 214(22), 212(44), 210(22), 189, 187(42), 107(100), 91(44), 79(51).

Preparation of endo- and exo-7-bromo-7-thiomethyl-1-methylbicyclo[4.1.0]-heptanes (12).

To 13.4 gm (50 mmol) of 11 in 150 mL of anhyd. ether at -105° under argon were added 25 mL (60 mmol) of 2.4 M n-butyllithium in hexane over a period of 20 min with the reaction temperature maintained below -98°. The reaction mixture was stirred for a further 40 min at -100° prior to addition of 7 mL (79 mmol) of dimethyldisulfide. The solution was stirred at -100° for 30 min, then allowed to gradually warm to r.t. overnight while remaining under an argon atmosphere. The reaction was terminated by addition of 300 mL of water, then extracted with pentane (2 × 200 mL). The combined pentane extracts were washed with 1 M Na₂CO₃ (2 × 150 mL), dried over anhyd. Na₂SO₄, filtered, and concentrated in vacuo to yield after distillation 10.2 gm (87%), b.p. 63-69°, 0.1 mm Hg (lit.^{17c} b.p. 85°, 5 mm Hg); ¹H NMR (60 MHz, CDCl₃), δ 2.23 (3H, SCH₃, s), 1.38 (3H, CH₃, s),

0.96-1.83 (9H, C₂-C₆, m).

Preparation of endo- and exo-1-methyl-7-carbomethoxy-7-thiomethyl-bicyclo[4.1.0]heptanes (13).

Under argon, 34 mL (82 mmol) of 2.4 M n-butyllithium in hexane were added at 0° to 9.4 gm (40 mmol) of 12 in 200 mL of hexane. The resultant solution was stirred at 0° for 45 min. The argon was then supplanted by a flow of CO₂ and the reaction was subsequently stirred at 0° for 30 min and an additional 4 hr while warming to r.t. The white, flocculent reaction mixture was then combined with 300 mL of 1 M Na₂CO₃ and washed with hexane (2 × 150 mL). The aqueous layer was then acidified to pH ≈ 2 by addition of conc. HCL and extracted with ether (3 × 150 mL). The combined ether extracts were dried over anhyd. Na₂SO₃, filtered, and combined with a freshly prepared ether solution of diazomethane. The resultant solution was dried over anhyd. MgSO₄, filtered, and concentrated in vacuo to yield after distillation 4.7 gm (55%), b.p. 70-76°, 0.2 mm Hg. The predominant stereoisomer is the exo-sulfide, in a ratio of >12:1, as determined by GC (Column B). Mass spectrum m/e (relative intensity) 214(30), 182(55), 154(5), 140(10), 139(100); ¹H NMR (400 MHz, CDCl₃) δ 3.75 (3H, OCH₃, s), 2.18 (3H, SCH₃, s), 1.93 (4H, 2CH₂, m), 1.60 (2H, CH₂, m), 1.42 (3H, CH₃, s), 1.23 (2H, CH₂, m), 1.10 (1H, CH, dd, J=2, 8 Hz)

HRMS Calcd. for C₁₁H₁₈O₂S: 214.1027. Found: 214.1021.

Preparation of endo- and exo-1-methyl-7-hydroxymethyl-7-thiomethyl-bicyclo[4.1.0]heptanes (14).

A solution of 1.71 gm (8 mmol) of 13 in 20 mL of ether was added dropwise at r.t. to a rapidly stirred suspension of 1.9 gm (50 mmol) of LiAlH₄

in 75 mL of ether and maintained at reflux for an additional 40 min. After cooling to r.t., the excess hydride was consumed by dropwise addition of ethyl acetate. Following addition of 20 mL of 20% NaOH, then 70 mL of water, the products were extracted with ether (3 × 70 mL). The combined ether extracts were dried over anhyd. Na₂SO₄, filtered, and concentrated in vacuo to yield after distillation 1.42 gm (95%), b.p. 84-89°, 0.2 mm Hg.

The predominant stereoisomer is the exo-sulfide, in a ratio of >14:1, as determined by GC (Column B). Mass spectrum m/e (relative intensity) 186(3), 171(36), 153(100), 95(27), 88(30), 81(26), 44(41); ¹H NMR (400 MHz, CDCl₃) δ 3.74 (1H, CHOH, dd, J=12, 5 Hz), 3.65 (1H, CHOH, dd, J=12, 7 Hz), 2.50 (1H, OH, dd, J= 5, 7 Hz), 2.07 (3H, SCH₃, s), 1.1-1.9 (8H, 4CH₂, m), 1.42 (3H, CH₃, s), 0.93 (1H, CH, dd, J= 9, 3 Hz).

HRMS Calcd. for C₁₀H₁₈OS: 186.1078. Found: 186.1087.

Preparation of 1-methylbicyclo[4.2.0]octan-7-one (15) and 6-methylbicyclo[4.2.0]octan-7-one (16).

To 930 mg (5 mmol) of 14, in 40 mL of methylene chloride under argon were added 9 mL (9 mmol) of 1.0 M triethyloxonium tetrafluoroborate in methylene chloride. The reaction was stirred at r.t. for 23 hr under argon, prior to addition of 30 mL (15 mmol) of 0.5 M NaOH. The resultant two-phase reaction mixture was stirred an additional 24 hr at r.t. The reaction was terminated by addition of 40 mL of water and extracted with 100 mL of pentane. The organic extract was dried over anhyd. MgSO₄, filtered, and concentrated by distillation at atmospheric pressure. Distillation under vacuum gave 472 mg (69%) of a mixture of 15 and 16, in a ratio of 3.7:1, by GC (Column B), b.p. 78-82°, 11 mm Hg. Analytical samples of the individual ketones were obtained by preparative GC (Column E) and gave

spectral data in agreement with those obtained by previous methods⁷⁶.

For 15 (slow eluting, major product): mass spectrum m/e (relative intensity) 138(69), 123(94), 95(100), 67(53); ¹H NMR (60 MHz, CDCl₃) δ 2.8 (3H, C₆ and C₈, m), 1.2-1.7 (11H, C₂-C₅ and C₉, m).

For 16 (faster eluting, minor product): mass spectrum m/e (relative intensity) 138(16), 123(2), 95(100), 67(35); ¹H NMR (60 MHz, CDCl₃) δ 2.5 (2H, C₈, m), 1.2-1.9 (12H, C₁-C₅ and C₉, m).

Preparation of syn- and anti-2,2,6-trimethyl-4-methoxy-7,7-dibromo-3-oxabicyclo[4.1.0]heptanes (17).

To a solution of 700 mg (2 mmol) of cetyltrimethylammonium bromide, 31.2 gm (0.2 mol) of 3, 100 mL (292 gm, 1.11 mol) of bromoform and 25 mL of benzene was added a chilled 50% NaOH solution (100 gm NaOH in 100 mL H₂O). The two-phase reaction mixture was stirred vigorously at r.t. for ≈170 hr. The reaction was terminated by dilution with 300 mL of water and extracted with ether (2 × 200 mL). The extracts were combined and washed with water (2 × 200 mL). Formation of an emulsion necessitated filtration through a pad of Celite and back-extraction of the aqueous phase with an additional 150 mL of ether. The combined organic extracts were dried over anhyd. MgSO₄, filtered, concentrated in vacuo, and distilled from KOH pellets to yield 49.1 gm (75%), b.p. 93-98°, 0.4 mm Hg; mass spectrum m/e (relative intensity) 296(4), 298, 294(2), 217, 215(10), 136(100), 93(12), 91(12), 78(25); chemical ionization (CH₄) 299, 297, 295(M⁺+1); ¹H NMR (60 MHz, CDCl₃) δ 4.59 (1H, O-CH-O, m), 3.25 (3H, OCH₃, s), 2.15 (2H, CH₂, m), 1.43 (3H, CH₃, s), 1.41 (3H, CH₃, s), 1.35 (3H, CH₃, s), 1.12 (1H, CH, s).

HRMS Calcd. for C₉H₁₂OBr₂(M⁺-MeOH): 297.9214, 295.9234, 293.9255.

Found: 297.9228, 295.9231, 293.9241.

Preparation of syn- and anti-2,2,6-trimethyl-4-methoxy-7,7-dichloro-3-oxabicyclo[4.1.0]heptanes (18).

To a solution of 31.2 gm (0.2 mol) of 3 in 120 mL of chloroform were added 700 mg (2 mmol) of cetyltrimethylammonium bromide and a chilled 50% NaOH solution (100 gm NaOH in 100 mL H₂O). The two-phase reaction mixture was stirred vigorously at r.t. for 21 hr. The reaction was terminated by dilution with 400 mL of water and extracted with methylene chloride (3 × 100 mL). The combined extracts were washed with water (2 × 150 mL), with the addition of small amounts of MgSO₄ to break emulsions formed during washing. The extract was then dried over anhyd. MgSO₄, filtered, concentrated in vacuo, and distilled to yield 44.2 gm (92%), b.p., 62-72°, 0.1 mm Hg (lit.⁷ b.p. 60-70°, 0.1 mm Hg).

Preparation of 2,2,6-trimethyl-4-methoxy-7-chloro-7-thiomethyl-3-oxabicyclo[4.1.0]heptanes (19).

To 9.56 gm (40 mmol) of 18 in 140 mL of dry THF at -100° under argon were added 35 mL (56 mmol) of 1.6 M n-butyllithium in hexane over a period of 30 min. During the course of this addition and the subsequent 75 min of stirring, the reaction temperature was maintained at -98° to -90°. 6 mL (62 mmol) of dimethyldisulfide were then added to the reaction. The resultant solution was stirred an additional 30 min at -95°, then allowed to gradually warm to r.t. overnight, while remaining under an argon atmosphere. The reaction was terminated by addition of 300 mL of water and extracted with ether (3 × 100 mL). The combined organic extracts were washed with 1 M Na₂CO₃ (2 × 150 mL), dried over anhyd. MgSO₄, filtered, and concentrated in vacuo. Distillation from KOH pellets gave 8.97 gm (89%), b.p. 74-84°, 0.1 mm Hg; mass spectrum m/e (relative intensity) 221(34),

219(86), 199(67), 109(75), 107(100), 69(69); chemical ionization (CH₄) m/e 251, 253(M⁺+1); ¹H NMR (60 MHz, CDCl₃) δ 4.56 (1H, O-CH-O, m), 3.42 (3H, OCH₃, s), 2.31 (3H, SCH₃, s), 1.96 (2H, CH₂, m), 1.51 (3H, CH₃, s), 1.43 (3H, CH₃, s), 1.37 (3H, CH₃, s), 1.03 (1H, CH, s).

HRMS Calcd. for C₁₀H₁₆OSeI(M⁺-OMe): 219.0610. Found: 219.0602.

Preparation of 2,2,6-trimethyl-4-methoxy-7-carbomethoxy-7-thiomethyl-3-oxabicyclo[4.1.0]heptanes (20).

Under argon, 37.5 mL (60 mmol) of 1.6 M n-butyllithium in hexane were added at -5° to 7.5 gm (30 mmol) of 19 in 100 mL of hexane. The cooling bath was removed and the solution was stirred for 1 hr at r.t. The argon was then replaced by a flow of CO₂, which was bubbled through the solution for 90 min. It was necessary to reapply the cooling bath during the initial 10 min of CO₂ addition in order to maintain the reaction temperature below 40°. The reaction was terminated by addition of 150 mL of water. The layers were separated and the aqueous portion was washed with hexane (2 × 60 mL). The aqueous layer was then transferred to a beaker, magnetically stirred, and cooled in an ice bath. Then, 30 mL of 0.5 N HCl were slowly added to the rapidly stirred solution which was, in turn, extracted with methylene chloride (2 × 75 mL). These combined organic extracts were dried over anhyd. Na₂SO₄, filtered, esterified with freshly prepared diazomethane, then dried over anhyd. MgSO₄ and analyzed by GC (Column B). This sequence of protonation, extraction, and esterification was repeated four times. The first four of these five separate fractions were shown by GC analysis to contain the desired product and, consequently, were combined and concentrated in vacuo to give 3.91 gm of a yellow oil (crude yield: 48%). A small fraction of this residue, comprised

principally of two isomers in a 2.8:1 ratio (Column C), was saved for spectroscopic analysis. Mass spectrum m/e (relative intensity) 274(34), 242(16), 195(27), 169(46), 158(100), 157(54), 143(57), 109(42); ^1H NMR (400 MHz, CDCl_3) δ 4.71, 4.53 (1H, O-CH-O, m), 3.72, 3.69 (3H, $\text{CH}_3\text{O}-\text{C}=\text{O}$, s), 3.45, 3.36 (3H, CH_3O , s), 2.52 (1H, C_5 , m), 2.19, 2.16 (3H, CH_3S , s), 1.66 (1H, C_5 , m), 1.52 (3H, CH_3 , s), 1.40 (3H, CH_3 , s), 1.27 (3H, CH_3 , s), 1.09, 1.03 (1H, C_1 , m).

Preparation of 2,2,6-trimethyl-4-methoxy-7-hydroxymethyl-7-thiomethyl-3-oxabicyclo[4.1.0]heptanes (21).

A solution of 3.9 gm of 20 in 50 mL of ether was added dropwise at r.t. to a rapidly stirred suspension of 3.04 gm (80 mmol) of LiAlH_4 in 100 mL of ether, and maintained at reflux for an additional 2 hr. After cooling to r.t., excess hydride was consumed by dropwise addition of ethyl acetate. Following addition of 50 mL of 15% NaOH, then 100 mL of water, the products were extracted with ether (3 \times 90 mL). The combined ether extracts were dried over anhyd. Na_2SO_4 , filtered, and concentrated in vacuo. The product was purified by a modification of Still's column chromatography procedure, as before, to yield 3.35 gm (45% from α -chlorosulfide, 19), >95% pure by GC of a mixture of two isomers in a 2.9:1 ratio (Column C); mass spectrum m/e (relative intensity) 246(1), 173(86), 157(44), 141(93), 115(74), 113(100), 109(70), 81(67); ^1H NMR (400 MHz, CDCl_3) δ 4.66, 4.56 (1H, O-CH-O, m), 3.98, 3.80 (1H, CH_2OH , m), 3.93, 3.74 (1H, CH_2OH , m), 3.41, 3.35 (3H, CH_3O , s), 2.13 (1H, C_5 , m), 2.08, 2.07 (3H, CH_3S , s), 1.71 (1H, C_5 , m), 1.58 (1H, OH, m), 1.49 (3H, CH_3 , s), 1.47 (3H, CH_3 , s), 1.18 (3H, CH_3 , s), 1.00, 0.80 (1H, C_2H , s).

HRMS Calcd. for $\text{C}_{12}\text{H}_{22}\text{O}_3\text{S}$: 246.1290. Found: 246.1293.

Attempted ring expansion of 21 to fused cyclobutanone: Preparation of 3,3,9-trimethyl-5-thiomethyl-2,7-dioxatricyclo[3.3.1.0^{4,5}]nonane (23).

To 100 mg (0.4 mmol) of 21, in 5 mL of methylene chloride under argon was added 1 mL (1 mmol) of 1.0 M triethyloxonium tetrafluoroborate in methylene chloride. The reaction was stirred at r.t. for 21 hr under argon prior to addition of 7 mL (3.5 mmol) of 0.5 M NaOH. The resultant two-phase reaction mixture was stirred an additional 8 hr at r.t. The reaction was terminated by addition of 25 mL of water and extracted with methylene chloride (2 × 20 mL). The organic extract was dried over anhyd. Na₂SO₄, filtered, and concentrated in vacuo. The product was purified by preparative TLC (hex.:EtOAc, 4:1) to yield 74 mg (85%); mass spectrum m/e (relative intensity) 214(45), 199(8), 167(32), 113(100), 109(41); ¹H NMR (400 MHz, CDCl₃) δ 5.10 (1H, C₁H, t, J=2.5 Hz), 4.26 (1H, C₆H, d, J=11 Hz), 4.21 (1H, C₆H, d, J=11 Hz), 2.13 (3H, CH₃S, s), 1.91 (2H, CH₂, d, J=2.5 Hz), 1.41 (3H, CH₃, s), 1.38 (3H, CH₃, s), 1.33 (3H, CH₃, s), 1.15 (1H, C₄H, s).

HRMS Calcd. for C₁₁H₁₈O₂S: 214.1027. Found: 214.1023.

Preparation of 2,2,4-trimethyl-5,6-dihydro-2H pyran (24).

A mixture of 98 gm (0.7 mol) of 5-hydroxy-3,5-dimethyl-3-hexenoic acid lactone in 20 mL of ether and 80 mL of THF was added dropwise to a rapidly stirred suspension of 19 gm (0.5 mol) of LiAlH₄ in 100 mL of THF at -35°. The reaction was allowed to warm to r.t. and was stirred for an addition 2 hr. Excess hydride was consumed by dropwise addition of ethyl acetate and the reaction mixture was poured into 1 L of ice containing 150 mL of conc. H₂SO₄. After stirring for 1 hr, the layers were separated and the aqueous phase extracted with ether (2 × 200 mL). The combined ether

extracts were washed with saturated NaHCO_3 (2×120 mL), then 100 mL of saturated NaCl , dried over anhyd. MgSO_4 , and filtered. Distillation at atmospheric pressure gave 74.7 gm (85%), b.p. $134-136^\circ$; mass spectrum m/e (relative intensity) 126(3), 111(100), 43(7); $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 5.29 (1H, $\text{C}=\text{CH}$, m), 3.78 (2H, OCH_2 , t, $J=5.5$ Hz), 1.93 (2H, CH_2 , m), 1.67 (3H, $\text{C}=\text{C}-\text{CH}_3$, d, $J=1.4$ Hz), 1.20 (6H, 2CH_3 , s).

Anal. Calcd. for $\text{C}_8\text{H}_{14}\text{O}$: C, 76.14; H, 11.18. Found: C, 76.31; H, 11.03.

Preparation of 2,2,6-trimethyl-7,7-dichloro-3-oxabicyclo[4.1.0]heptane (25).

To a solution of 54 gm (0.43 mol) of 24 in 200 mL of chloroform was added 1.4 gm (4 mmol) of cetyltrimethylammonium bromide and a chilled 50% NaOH solution (180 gm NaOH in 180 mL H_2O). The two-phase reaction mixture was stirred vigorously for 1 hr in an ice bath, then 21 hr at r.t. The reaction was terminated by dilution with 700 mL of water and extracted with methylene chloride (2×250 mL). The combined organic extracts were washed with 2×400 mL of water (emulsions that formed were broken by filtration through a pad of Celite), dried over anhyd. MgSO_4 , filtered, and concentrated in vacuo. Distillation under vacuum gave 78.8 gm (88%), b.p. $63-66^\circ$, 0.6 mm Hg; mass spectrum m/e (relative intensity) 212, 210, 208(<1), 152(90), 150(100), 117(51), 115(93), 79(95); $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 3.54 (1H, C_4H eq', ddd, $J=12.1, 7, 0.9$ Hz), 3.49 (1H, C_4H ax', ddd, $J=12.1, 12.9, 4.2$ Hz), 2.16 (1H, C_5H ax', ddd, $J=7, 12.9, 14.7$ Hz), 1.50 (1H, C_5H eq', ddd, $J=0.9, 4.2, 14.7$ Hz), 1.47 (3H, CH_3 , s), 1.44 (3H, CH_3 , s), 1.29 (3H, CH_3 , s), 1.02 (1H, C_1H , s).

HRMS Calcd. for $\text{C}_9\text{H}_{14}\text{OCl}_2$: 208.0422. Found: 208.0421.

Preparation of endo- and exo-2,2,6-trimethyl-7-chloro-7-thiomethyl-3-oxa-bicyclo[4.1.0]heptanes (26).

To 16.72 gm (80 mmol) of 25 in 220 mL of dry THF at -105° under argon were added 40 mL (84 mmol) of 2.1 M n-butyllithium in hexane over a period of 35 min. During the course of this addition and the subsequent 90 min of stirring, the reaction temperature was maintained at -100° to -90° . Then 10 mL (113 mmol) of dimethyldisulfide were then added to the reaction. The resultant solution was stirred an additional 30 min at -95° , then allowed to gradually warm to r.t. overnight while remaining under an argon atmosphere. The reaction was terminated by dilution with 200 mL of water, and extracted with ether (3×100 mL). The combined ether extracts were washed with 1 M Na_2CO_3 (2×150 mL), dried over anhyd. MgSO_4 , filtered, and concentrated in vacuo. Distillation from KOH pellets gave 15.74 gm (89%), b.p. $65-70^{\circ}$, 0.3 mm Hg; mass spectrum m/e (relative intensity) 220, 222(1), 149(38), 147(100), 127(30), 115(24), 79(33); ^1H NMR (400 MHz, CDCl_3) δ 3.52 (2H, OCH_2 , m), 2.28, 2.20 (3H, CH_3S , s), 2.09 (1H, C_5H ax', m), 1.52 (1H, C_5H eq', m), 1.50 (3H, CH_3 , s), 1.43, 1.38 (3H, CH_3 , s), 1.32, 1.30 (3H, CH_3 , s), 1.22, 0.83 (1H, CH, s).

HRMS Calcd. for $\text{C}_{10}\text{H}_{17}\text{OSCl}$: 220.0689. Found: 220.0676.

Preparation of 2,2,6-trimethyl-7-carbomethoxy-7-thiomethyl-3-oxabicyclo[4.1.0]heptane (27).

Under argon 60 mL (126 mmol) of 2.1 M n-butyllithium in hexane were added at -5° to 14 gm (63.6 mmol) of 26 in 100 mL of hexane. The cooling bath was removed and the solution was stirred for 90 min at r.t. The argon was then replaced by a flow of CO_2 which was bubbled through the solution for 2 hr. It was necessary to reapply the cooling bath during the initial

15 min of CO₂ addition in order to maintain the reaction temperature below 30°. The reaction was terminated by dilution with 150 mL of water. The layers were separated and the aqueous phase was acidified to pH ≈ 2 by addition of conc. HCl and extracted with methylene chloride (3 × 70 mL). The combined methylene chloride extracts were dried over anhyd. Na₂SO₄, filtered, and combined with a freshly prepared ether solution of diazomethane. The resultant solution was dried over anhyd. MgSO₄, filtered, and concentrated in vacuo to give 8.56 gm of a yellow oil (crude yield 55%). A small portion of this residue was saved for analysis and purified by preparative TLC (hex.:EtOAc, 3:1; R_f = 0.53); mass spectrum m/e (relative intensity) 244(28), 171(82), 158(31), 154(73), 143(41), 139(100), 111(42), 79(49); ¹H NMR (400 MHz, CDCl₃) δ 3.70 (3H, CH₃O, s), 3.68 (1H, C₄H, ddd, J=11.8, 8.6, 7.7 Hz), 3.50 (1H, C₄H, ddd, J=11.8, 10.2, 3.5 Hz), 2.54 (1H, C₅H, ddd, J=7.7, 10.2, 14.4 Hz), 2.16 (3H, CH₃S, s), 1.56 (1H, C₅H, ddd, J=8.6, 3.5, 14.4 Hz), 1.41 (3H, CH₃, s), 1.38 (3H, CH₃, s), 1.28 (3H, CH₃, s), 1.04 (1H, C₁H, s).

Preparation of 2,2,6-trimethyl-7-hydroxymethyl-7-thiomethyl-3-oxabicyclo-[4.1.0]heptane (28).

A solution containing 8.5 gm (≈35 mmol) of the crude ester 27 in 80 mL of ether was added dropwise at r.t. to a rapidly stirred suspension of 3.4 g (90 mmol) of LiAlH₄ in 200 mL of ether. The reaction was refluxed for 2.5 hr. After cooling to r.t., excess hydride was consumed by dropwise addition of ethyl acetate. Following addition of 100 mL of 15% NaOH, then 200 mL of water, the product was extracted with ether (3 × 100 mL). The combined ether extracts were dried over anhyd. Na₂SO₄, filtered, and concentrated in vacuo. The product was purified by column chromatography, as

per alcohol 21, to give 7.56 gm (53% from α -chlorosulfide 26); mass spectrum m/e (relative intensity) 216(1), 143(100), 113(74), 111(87), 93(63), 81(57), 79(54), 55(59); ^1H NMR (400 MHz, CDCl_3) δ 3.99 (1H, C_4H , m), 3.87 (1H, C_4H , m), 3.52 (2H, CH_2OH , m), 2.05 (3H, CH_3S , s), 1.99 (1H, C_5H , m), 1.59 (1H, OH, m), 1.54 (1H, C_5H , m), 1.43 (3H, CH_3 , s), 1.30 (3H, CH_3 , s), 1.18 (3H, CH_3 , s), 0.78, 0.77 (1H, C_1H , s).

HRMS Calcd. for $\text{C}_{11}\text{H}_{20}\text{O}_2\text{S}$: 216.1184. Found: 216.1183.

Attempted ring expansion of 28 to fused cyclobutanone.

To 1.5 gm (7 mmol) of 28 in 20 mL of methylene chloride, under argon, were added 10 mL (10 mmol) of 1.0 M triethoxonium tetrafluoroborate in methylene chloride. The reaction was stirred at r.t. for 5 hr under argon, prior to addition of 25 mL (12.5 mmol) of 0.5 M NaOH. The resultant two-phase reaction mixture was stirred an additional 2 hr at r.t. The reaction was terminated upon addition of 100 mL of water and extracted with methylene chloride (3 \times 40 mL). The combined organic extracts were dried over anhyd. Na_2SO_4 and filtered. GC analysis (Column C) of the filtrate revealed complete consumption of the starting material, to give a myriad of products; none of which was greater than 10% of the mixture.

REFERENCES

1. a) J.H. Borden, R.G. Brownlee and R.M. Silverstein, *Can. Entomol.* 100, 629 (1968).
b) J.H. Borden and C.E. Slater, *Ann. Entomol. Soc. Am.* 62, 454 (1969).
2. a) J.A. Rudinsky and G.E. Daterman, *Z. Angew. Entomol.* 54, 300 (1964).
b) J.A. Rudinsky and G.E. Daterman, *Can. Entomol.* 96, 1339 (1964).
c) J.A. Chapman, *Can. Entomol.* 98, 50 (1966).
3. J.G. MacConnell, J.H. Borden, R.M. Silverstein and E. Stokkink, *Chem. Ecol.* 3, 549 (1977).
4. J.H. Borden, J.R. Handley, B.D. Johnston, J.G. MacConnell, R.M. Silverstein, K.N. Slessor, A.A. Swigar and D.T.W. Wong, *Chem. Ecol.* 5, 681 (1979).
5. a) K. Mori and M. Sasaki, *Tetrahedron Lett.*, 1329 (1979).
b) K. Mori and M. Sasaki, *Tetrahedron* 36, 2197 (1980).
6. J.H. Borden, A.C. Oehlschlager, K.N. Slessor, L. Chong and H.D. Pierce, Jr., *Can. Entomol.* 112, 107 (1980).
7. K.N. Slessor, A.C. Oehlschlager, B.D. Johnston, H.D. Pierce, Jr., S.K. Grewal and L.K.G. Wickremesinghe, *J. Org. Chem.* 45, 2290 (1980).
8. a) K. Mori, T. Uematsu, M. Minobe and K. Yanagi, *Tetrahedron Lett.* 23, 1921 (1982).
b) K. Mori, T. Uematsu, M. Minobe and K. Yanagi, *Tetrahedron* 39, 1735 (1983).
9. a) K. Graham, *Can. J. Zool.* 46, 905 (1968).
b) H.A. Moeck, *Can. Entomol.* 102, 985 (1970).

10. Mass trapping of T. lineatum using lineatin baited traps is commercially used in B.C.: J.H. Borden, A.C. Oehlschlager and S. Burke, private communication.
11. H.D. Pierce, Jr., private communication.
12. L. Skattebol and Y. Senstrom, *Tetrahedron Lett.* 24, 3021 (1983).
13. K.N. Slessor and B.D. Johnston. This approach was suggested at the Sixty-second Annual Conference of the C.I.C., Vancouver, B.C., June, 1979 (pheromone symposium).
14. W.R. McKay, J. Ounsworth, P. Sum and L. Weiler, *Can. J. Chem.* 60, 872 (1982).
15. B.M. Trost and W.C. Vladuchick, *Synthesis*, 821 (1978).
16. a) B.M. Trost and M.J. Bogdanowicz, *J. Am. Chem. Soc.* 95, 5321 (1973).
b) B.M. Trost, D.E. Keeley, H.C. Arndt and M.J. Bogdanowicz, *J. Am. Chem. Soc.* 99, 3088 (1977).
17. a) M. Braun and D. Seebach, *Angew. Chem. Int. Ed. (Eng.)* 13, 277 (1974).
b) M. Braun, R. Dammann and D. Seebach, *Chem. Ber.* 108, 2368 (1975).
c) M. Braun and D. Seebach, *Chem. Ber.* 109, 669 (1976).
18. A.B. Smith and R.M. Scarborough, *Synth. Comm.* 10, 205 (1980); see also L.M. Berkowitz and P.M. Rylander, *J. Am. Chem. Soc.* 80, 6682 (1958), and R.M. Moriarty, H. Gopaul and T. Adams, *Tetrahedron Lett.*, 4003 (1970).
19. F.G. Young, *J. Am. Chem. Soc.* 71, 1346 (1949).
20. K.S. Pillay, A.C. Oehlschlager and W.H. Romines, III, unpublished results.

21. a) E.J. Corey, C.S. Shiner and R.P. Volante, *Tetrahedron Lett.*, 1161 (1975).
- b) P.K. Freeman, D.M. Balls and D.J. Brown, *J. Org. Chem.* 33, 221 (1968).
22. D.A. Evans, W.L. Scott and L.K. Truesdale, *Tetrahedron Lett.*, 121 (1972).
23. K.S. Pillay, private communication.
24. R.M. Silverstein, private communication.
25. J.D. White, M.A. Avery and J.P. Carter, *J. Am. Chem. Soc.* 104, 5486 (1982).
26. D.H. Aue, M.J. Meshicknek and D.F. Shellhamer, *Tetrahedron Lett.*, 4799 (1973).
27. W.C. Still, M. Kahn and A. Mishra, *J. Org. Chem.* 43, 3923 (1978).
28. H. Kosugi, S. Sekiguchi, R. Sekita and H. Uda, *Bull. Chem. Soc. Jpn.* 49, 520 (1976).
29. L.R. Krepski and A. Hassner, *J. Org. Chem.* 43, 2879 (1978).
30. R. Matherbe, G. Rist and G. Bellus, *J. Org. Chem.* 48, 860 (1983).
31. B.D. Johnston, K.N. Slessor and A.C. Oehlschlager, manuscript in preparation.
32. A.C. Oehlschlager, private communication.
33. A. Kandil, private communication.
34. G. Stork and J.F. Cohen, *J. Am. Chem. Soc.* 96, 5270 (1974).
35. a) A.E. Green, J.C. Muller and G. Ourisson, *J. Org. Chem.* 39, 186 (1974).
- b) S.M. Ali and S.M. Roberts, *Chem. Comm.*, 887 (1975).

36. a) E. Baciocchi, S. Clementi, R. Ruzziconi and G.V. Sebastiani, *J. Heterocyclic Chem.* 14, 949 (1977).
b) M. Schlosser and T.D. An, *Helv. Chim. Acta* 62, 1194 (1979).
37. N.J. Turro, *Modern Molecular Photochemistry*, Benjamin-Cummings Publishing Co. (1978).
38. a) F.D. Lewis and R.H. Hirsch, *J. Am. Chem. Soc.* 98, 5914 (1976).
b) J. Michl, *Molec. Photochem.* 4, 257 (1972).
c) J.A. Baltrop and H.A.J. Carless, *J. Am. Chem. Soc.* 94, 1951 (1972).
39. a) V. Bonacic-Koutecky, P. Bruckmann, P. Hiberty, J. Koutecky, C. Leforestier and L. Salem, *Angew. Chem. Int. Ed. (Eng.)* 14, 575 (1975).
b) L. Salem and C. Rowland, *Angew. Chem. Int. Ed. (Eng.)* 11, 92 (1972).
40. S. Kuwata, Y. Shigemitsu and Y. Odaira, *J. Org. Chem.* 38, 3803 (1973).
41. D.R. Arnold and A.J. Maroulis, *J. Am. Chem. Soc.* 98, 5931 (1976).
42. a) P.A. Grutsch and C. Kutal, *J. Am. Chem. Soc.* 101, 4228 (1979).
b) R.G. Salomon, A. Sinha and M.F. Salomon, *J. Am. Chem. Soc.* 100, 520 (1978).
c) R.G. Salomon and A. Sinha, *Tetrahedron Lett.*, 1367 (1978).
43. R.G. Salomon, D.J. Coughlin, S. Ghosh and M.G. Zagorski, *J. Am. Chem. Soc.* 104, 998 (1982).
44. a) R.G. Salomon, *Tetrahedron* 39, 485 (1983).
b) R.G. Salomon, D.J. Coughlin and E.M. Easler, *J. Am. Chem. Soc.* 101, 3961 (1979).

45. a) R.G. Salomon and J. Kochi, *J. Am. Chem. Soc.* 95, 1889 (1973).
b) T. Cohen and R.J. Ruffner, *Org. Syn.* 59, 202 (1980).
46. C.L. Jenkins and J.K. Kochi, *J. Am. Chem. Soc.* 94, 843 (1972).
47. a) J.K. Kochi, A. Bemis and C.L. Jenkins, *J. Am. Chem. Soc.* 90, 4616 (1968).
b) R.G. Salomon and J.K. Kochi, *J. Am. Chem. Soc.* 95, 3300 (1973).
c) C.L. Jenkins and J.K. Kochi, *J. Am. Chem. Soc.* 94, 846 (1972).
48. a) E.J. Corey, R. Mitra and H. Uda, *J. Am. Chem. Soc.* 86, 485 (1964).
b) E.J. Corey, J.D. Bass, R. LeMahieu and R. Mitra, *J. Am. Chem. Soc.* 86, 5570 (1964).
49. C.S. Shiner, A.M. Fisher and F. Yacoby, *Tetrahedron Lett.* 24, 5687 (1983).
50. A.M. van Leusen and D. van Leusen, *Syn. Comm.* 8, 397 (1978).
51. a) P.A. Grieco and K. Hiroi, *Tetrahedron Lett.*, 3467 (1974).
b) Y. Tsuda, T. Tanno, A. Ukai and K. Isobe, *Tetrahedron Lett.*, 2009 (1971).
52. W.R. Moser, *J. Am. Chem. Soc.*, 91, 1135 (1969).
53. D.J. Cram, *Fundamentals of Carbanion Chemistry*, Academic Press (1965).
54. H.W. Pinnick, Y.H. Chang, S.C. Foster and M. Govindan, *J. Org. Chem.* 45, 4505 (1980).
55. a) G.A. Russell, M. Makosza and J. Herschberger, *J. Org. Chem.* 44, 1195 (1979).
b) B.J. Fitzsimmons and B. Fraser-Reid, *J. Am. Chem. Soc.* 101, 6123 (1979).

56. a) P.M. Warner and D. Le, J. Org. Chem. 47, 893 (1982).
b) E.G.E. Jähren, D. Phillips, R.J. Kobelski and D.M. Demko, J. Org. Chem. 48, 2472 (1983).
57. a) M. Jones, W. Ando and A. Kulczyski, Tetrahedron Lett., 1391 (1967).
b) M.E. Hendrick, J. Am. Chem. Soc. 93, 6337 (1971).
58. A.J. Anciaux, A.J. Hubert, A.F. Noels, N. Pertinot and P. Teyssie, J. Org. Chem. 45, 695 (1980).
59. R. Paulissen, A.J. Hubert and P. Teyssie, Tetrahedron Lett., 1465 (1972).
60. a) R.A. Moss and F.B. Pilkiewicz, Synthesis, 209 (1973).
b) R.A. Moss, M.A. Joyce and F.G. Pilkiewicz, Tetrahedron Lett., 2425 (1975).
61. M. Makosza and M. Wawrzyniewicz, Tetrahedron Lett., 4659 (1969).
62. B.M. Trost, private communication.
63. a) B.M. Trost and Y. Tamaru, J. Am. Chem. Soc. 97, 3528 (1975).
b) J.R. Shanklin, C.R. Johnson, J. Ollinger and R.M. Coates, J. Am. Chem. Soc. 95, 3429 (1973).
64. B.M. Trost and L.N. Tungheim, J. Am. Chem. Soc. 102, 7910 (1980).
65. a) P.M. Warner and R.D. Herold, J. Org. Chem. 48, 5411 (1983).
b) G. Kobrich and W. Goyert, Tetrahedron 24, 4327 (1968).
c) D. Seyferth and R.L. Lambert, J. Organomet. Chem. 88, 287 (1975).
66. a) K. Kitatani, T. Hiyama and H. Nozaki; Bull. Chem. Soc. Jpn. 50, 3288 (1977).
b) M. Schlosser and J. Hartmann, J. Am. Chem. Soc. 98, 4674 (1976).

67. R.M. Silverstein, G.C. Bassler and T.C. Morrill, Spectrometric Identification of Organic Compounds (4th Edition), John Wiley & Sons (1981); see also F.A.L. Arnet, S. Winstein, P. Carter and A.J.R. Bourn, J. Am. Chem. Soc. 87, 5247, 5249 (1965).
68. F.A.L. Arnet and A.J.R. Bourn, J. Am. Chem. Soc. 87, 5250 (1965).
69. L. Skattebol and S. Solomon, Org. Syn. 49, 35 (1969).
70. a) T. Hiyama, A. Kanakura, H. Yamamoto and H. Nozaki, Tetrahedron Lett., 3047 (1978).
b) K.G. Taylor, W.E. Hobbs, M.S. Clark and J. Chaney, J. Org. Chem. 37, 2436 (1972).
71. a) M.E. Garst, B.J. McBride and A.T. Johnson, J. Org. Chem. 48, 8 (1983).
b) J.L. Kice and C.A. Liu, J. Org. Chem. 44, 1918 (1979).
c) B.M. Trost and E. Murayama, J. Am. Chem. Soc. 103, 6529 (1981).
d) W.N. Olmstead and L.I. Braumann, J. Am. Chem. Soc. 99, 4219 (1977).
72. E.M. Burgess, H.R. Renton and E.A. Taylor, J. Org. Chem. 38, 26 (1973).
73. T. Cohen and J.R. Matz, Tetrahedron Lett. 22, 2455 (1981).
74. These two syntheses are, in fact, applicable to commercial scale production of the pheromone: Johnston's synthesis (Scheme J) has supplied lineatin for commercial use in Canada and the U.S. and Skattebol's synthesis (Scheme K) is being adapted by Borregaard of Norway for commercial use in Europe³².
75. H.H. Wasserman, M.J. Hearn, B. Haveaux and M. Thyges, J. Org. Chem. 41, 153 (1976).

76. D.A. Bak and W.T. Brady, J. Org. Chem. 44, 107 (1979).