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# Synthetic approaches to the furanosesquiterpenes

William Ellis Delaney III
*Iowa State University*

# Synthetic approaches to the furanosesquiterpenes

by

William Ellis Delaney III

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1973

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DEDICATION

To my wife, Pam,

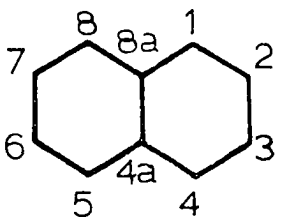
whose love and encouragement over

the past five years made this work possible.

# NOMENCLATURE OF NAPHTHALENE DERIVATIVES

The nomenclature system that is currently employed by Chemical Abstracts has been selected for use in this manuscript. Since this system is decidedly more cumbersome than the commonly used system based on the trivial name "decalin", this section will serve as as explanation of the Chemical Abstracts nomenclature. For additional information the reader may consult references (1-4).

A. Numbering: The numbering system employed in this manuscript and in Chemical Abstracts is illustrated below.




B. Naphthalenone derivatives:

1. These compounds are named as derivatives of the completely saturated ring system: 1,2,3,4,4a,5,6,7,8,8a-decahydronaphthalenone.

2. The substituents are listed in alphabetical order without considering prefixes such as di, tri, hexa, octa, etc.

3. The "indicated hydrogen" is given the lowest possible number consistent with a chemically reasonable parent compound.

4. Relative stereochemistry in cyclic systems is designated by Beilstein's system using c, t, and r descriptors. The lowest numbered substituent is assigned the letter r (reference). Groups on the same side of the ring as the reference group are designated c (cis); groups on the opposite side of the ring are designated t (trans).

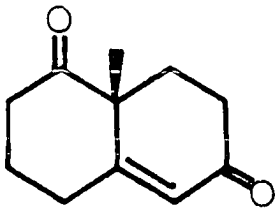
5. Cis or trans preceding the name of the compound indicates the stereochemistry at the ring fusion; i. e., the relationship of the substituents at 4a and 8a. The prefix dl is omitted from the names of racemic compounds.

C. Benzofuran and naphthofuran derivatives:

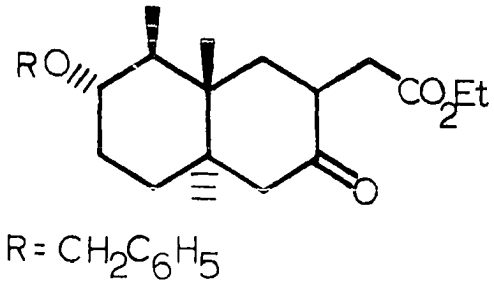
1. The compounds in this manuscript containing the furan ring are either [2,3-b]naphthofuran derivatives or benzofuran derivatives. These compounds are again named as derivatives of the completely saturated system: 2,3,3a,4,4a,5,6,7,8,8a,9,9a-dodecahydronaphtho[2,3-b]furan.

2. All other rules are the same as rules (2-5) above.

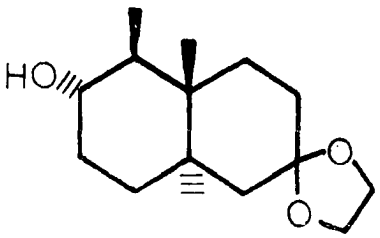
D. Examples:



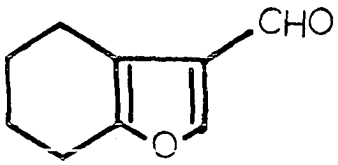
3,4,8,8a,-tetrahydro-8a-methyl-1,6(2H,7H)-naphthalenedione




ethyl 2-(trans-r-7-benzyloxy-decahydro-t-8,t-8a-dimethyl-3-oxo-2-naphthalenyl) acetate




trans-6,6-ethylenedioxy-decahydro-r-1,c-8a-dimethyl-t-2-naphthol




4,5,6,7-tetrahydro-3-benzofurancarboxaldehyde

# INTRODUCTION

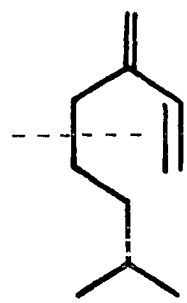
Man, throughout recorded time, has been interested in scents and perfumes. He has used them in foods, on the hair or body and in primitive, and even modern medicines. By far the greatest source of these scents is in the plants. It was discovered that when fragrant plants were crushed and heated, the odors could be condensed on a cool surface as oils and water soluble liquids. In time these became known as "essential oils". The term "essential oils" is still in use today although we now include in this category materials obtained by other methods: steam distillation, extraction, expression, and chromatography.

Chemical investigation of the essential oils was inevitable and began at the beginning of the nineteenth century, probably by Dumas (deMayo (5)). It was then found that essential oils contained numerous hydrocarbons each made up of ten carbons; these compounds became known as the terpenes (German-turpentine). Other compounds were isolated; some contained oxygen, some contained other functional groups; but all contained ten carbons. These became known as the terpenoids. Today this term is generally used to describe this class of compounds, whether or not they are hydrocarbons. Finally, as attention became focused on higher boiling components of the essential oils, other similar classes of compounds were discovered. These became known as

the sesquiterpenes, fifteen carbons; the diterpenes, twenty carbons; the triterpenes, thirty carbons and the tetraterpenes, forty carbons.

Early stages of investigation revealed that the terpenoids are, in general, built up in units of five carbon atoms, each unit based on the structure of isoprene (1). This observation led to the formulation of the "isoprene rule", that is, that a terpenoid carbon skeleton could be formally divided into isoprene units (6). In most cases the isoprene units are linked in a head to tail fashion as shown below for myrcene (2) and selinene (3).

1



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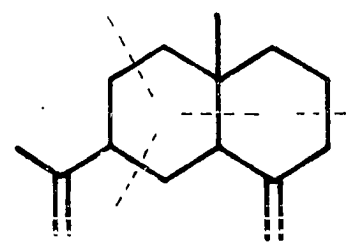

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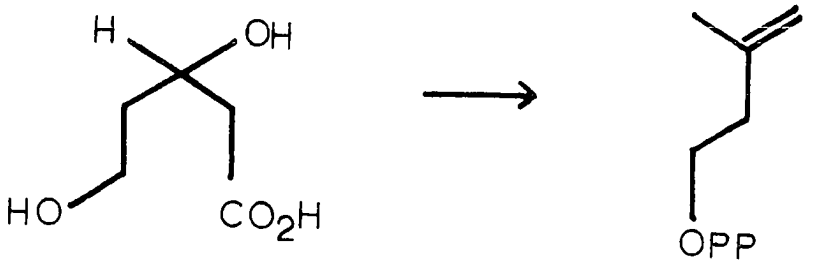
This view of the relationship of isoprene to the terpenoids is only a formal one, however, as isoprene itself is not known to be a naturally occurring compound.

Biosynthetically, instead of isoprene, it is now generally held that the building block for the terpenes is mevalonic acid (4) which leads—after three phosphorylations,

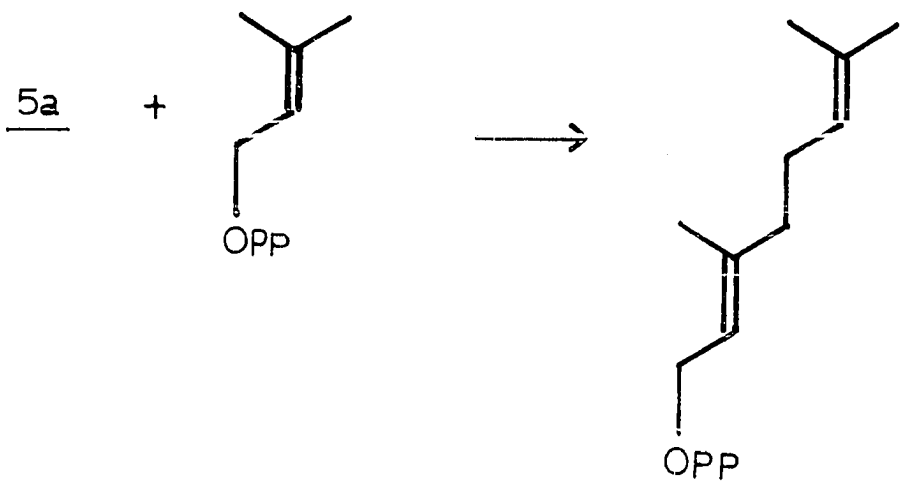
a concerted elimination and decarboxylation, and a double bond migration—to the active intermediate, 3-isopentenyl pyrophosphate (5a). It is the condensation of 3-isopentenyl pyrophosphate (5a) with dimethylallyl pyrophosphate (5b), that yields geranyl pyrophosphate (6) which can then cyclize, oxygenate or rearrange to any of the acyclic or cyclic monoterpenoids. Alternatively the dimer, geranyl pyrophosphate (6) may continue to add additional 3-isopentenyl pyrophosphate units (5a) to build up the sesqui-, di-, tri-, or tetraterpene skeleton. The cyclizations and rearrangements of these units are believed to result from loss of pyrophosphate to yield an allylic carbonium ion which then rearranges. Alternatively, farnesyl pyrophosphate, the trimer, may also cyclize to a substituted cyclodecene. Subsequent intramolecular cyclization would give either the hydronaphthalene or hydroazulene sesquiterpenes. These reactions are summarized in Scheme I.

Several good texts have been written dealing with the structure, isolation and occurrence of the terpenes. The author especially recommends the works of deMayo (5), Pinder (7), Simonsen and Barton (8), and Templeton (9). For a discussion of the biochemical aspects of the terpenes, a good general biochemistry textbook may suffice; the author is familiar with White, Handler, and Smith (10) and Mahler and Cordes (11).

Scheme I



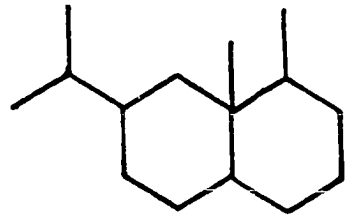

4 5a




5b 6

This manuscript is concerned with a single segment of terpene chemistry, the synthesis of sesquiterpenes; in particular, those containing as part of their skeleton, the furan ring.

One class of sesquiterpenes, the eremophilanes (12) is unique in that the basic carbon skeleton cannot be divided into three isoprene units. These compounds, then, are "non-isoprenoid" sesquiterpenes and exhibit the skeletal structure shown below.



In 1966 a communication (13) was published describing the isolation, from the wood of an East African tree, of a furanosesquiterpene of the eremophilane class. This compound was named "warburgin". Since the synthesis of this compound involved two interesting features: namely, the furan ring and the non-isoprenoid skeleton; it appeared to be an exciting problem, the approaches to which form the subject of this manuscript.

# HISTORICAL

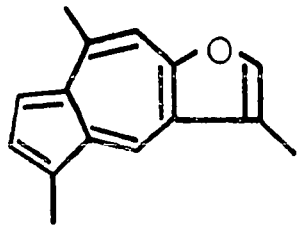
The first investigations on the chemistry of the furanosesquiterpenes took place just before 1930 when Suzuki (14) began his work on the Chinese drug "T'ien t'ai wu yao". Ether extracts of the drug, from the dried root of the evergreen shrub Lindera strychnifolia Vill., were distilled; and the main component, which Suzuki named "linderene", was isolated.

Although the structure of linderene was not known, Kondo and Takeda (15) in 1939, succeeded in dehydrogenating a sample to the azulene (7), which they named linderazulene. In 1953 Takeda (16) proposed structure 8 for linderene.

Takeda and his associates at Shionogi Reasearch Labs; Osaka, Japan, have since then undertaken extensive investigation into the chemistry of Lindera strychnifolia Vill., and several related plants.

When the structure of linderazulene was accurately determined by synthesis (16,17) Tada et al., revised the structure of linderene (8) to that shown in structure 9 and renamed it lindenenol (18,19).

From the extracts of Suzuki's samples, they subsequently isolated six other sesquiterpenes, all containing the furan ring. They named these: lindenene (10), (20), linderoxide (11), (21), isogermafurene-later renamed isofuranogermacrene (12), (21,22), isolinderoxide (13), (23), lindenenone (14),



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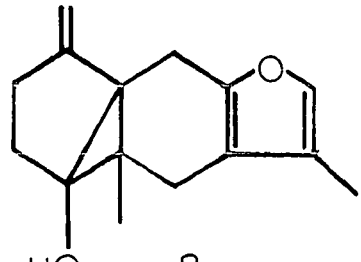

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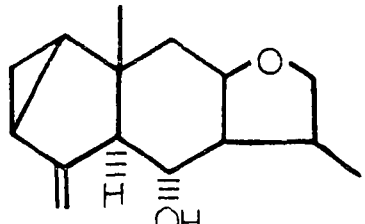

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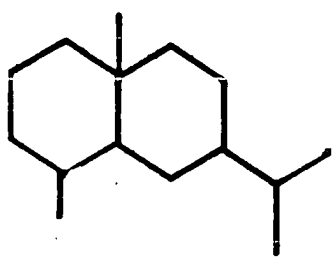
(24,25) and neolinderalactone (15), (24). These seven compounds were isolated from the plant of Chinese origin; however when the same plant was collected in Japan and examined, a number of new furanosesquiterpenes were isolated and identified. These were, in addition to lindenenol, linderane (16), (26,27), linderalactone (17), (27,28), isolinderalactone (18), (25,28), lindestrene (19), (29) and lindenenol acetate (20), (19).

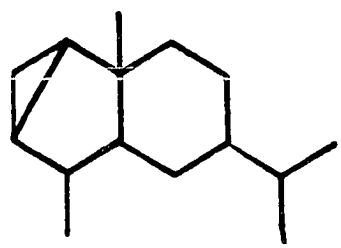
The observation that these two samples contained different sesquiterpenes led to a comparison study of Lindera strychnifolia Vill., obtained from four different sources: two from China and one each from Formosa and Japan. The study showed that, while most of the same compounds were present in samples from each source, the amounts varied con-

siderably (30).

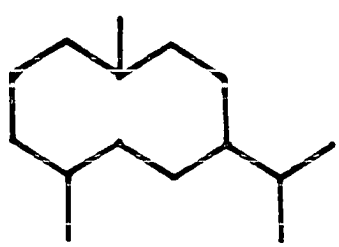
Finally the discovery of pseudoneolinderane (21), (31) and epidihydroisolinderalactone (22), (32) in 1968 and the isolation of neosericenyl acetate (23), (17) in 1971 has brought the total number of furanosesquiterpenes in Lindera to fifteen. They have been classified by the four main structure types: selinane, lindenane, germacrane, and ellemane whose basic skeletal structures are shown below.



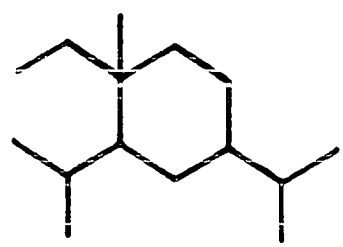
SELINANE



LINDENANE



GERMACRANE



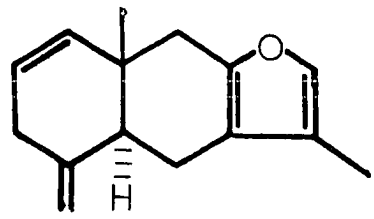
ELLEMANE

Chart I summarizes the fifteen Lindera furanosesquiterpenes and shows their structures by type.

In addition to Lindera strychnifolia Vill., three other members of the Lauraceae family have been found to contain furanosesquiterpenes: Neolitsea aciculata Koidz., Neolitsea

Chart I

Selinane:



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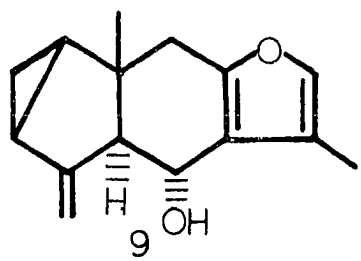
Lindenane:



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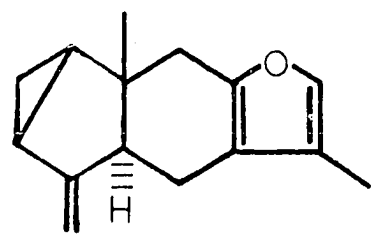

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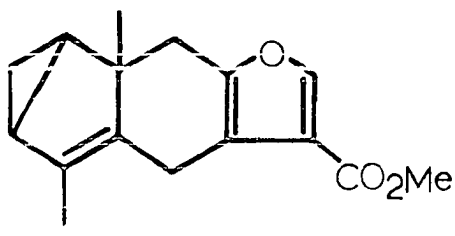

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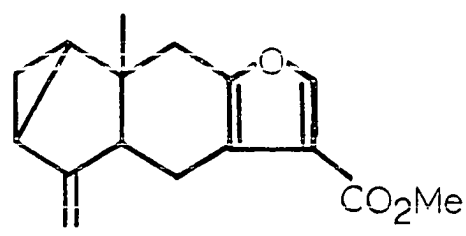

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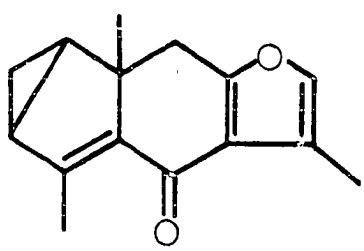

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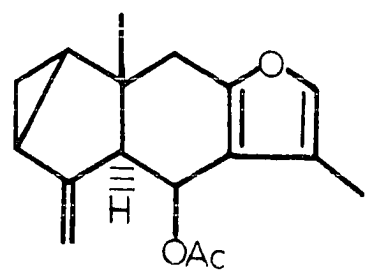

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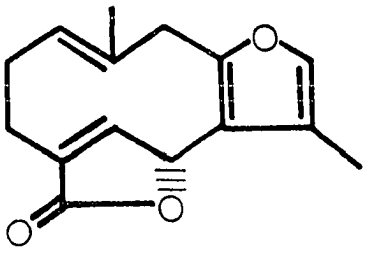
Chart I (Cont.)

Germacrane:



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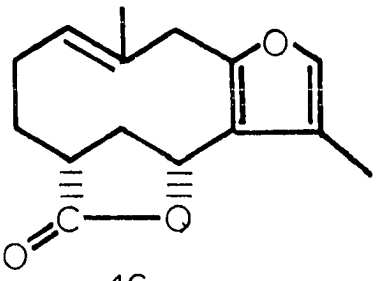

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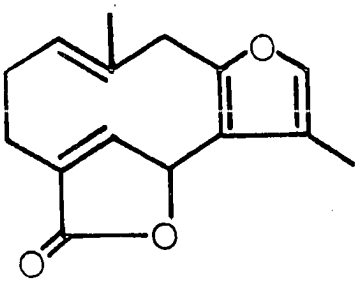

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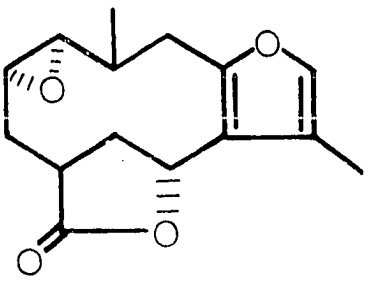

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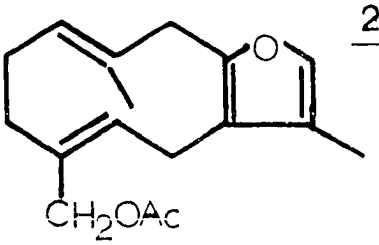

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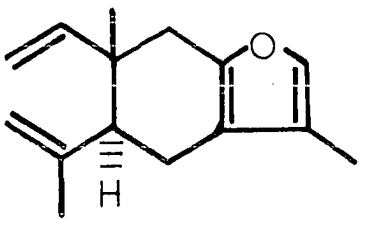
Ellemane:



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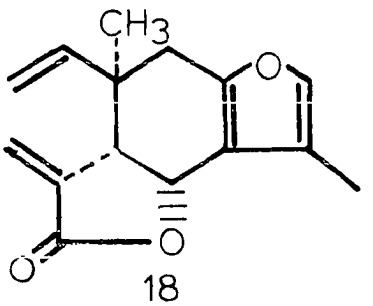

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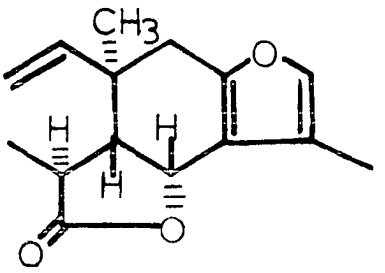
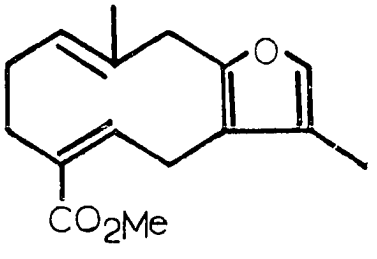


sericea Koidz., and Neolitsea zeylanica Merr.

Hayashi et al., have recently isolated several furanosesquiterpenes of the ellemane and germacrane types from the leaf of Neolitsea sericea Koidz. They determined the structures of sericenine (24) and sericenic acid (25), (17). Isosericenine (26) (34) was also reported. Takeda (35) reports that examination of the root of the same plant reveals the presence of lindestrene, lindenene, linderalactone and isolinderalactone. He also found, in the leaf, a new compound neosericenine (27), (36).

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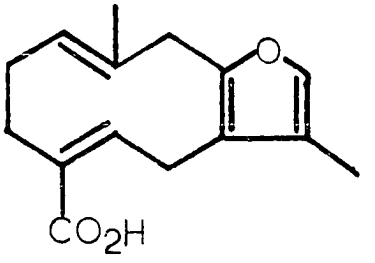


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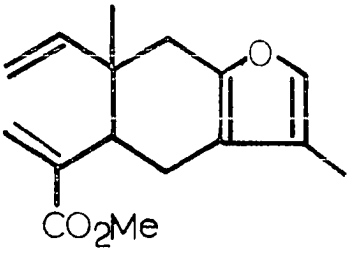


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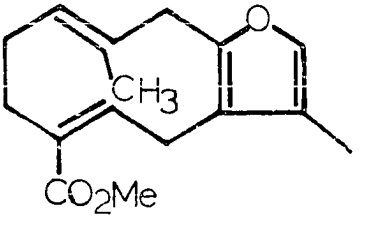


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Neolitsea aciculata Koidz., has been investigated and ten furan containing sesquiterpenes have been isolated (37). Five of these ten were known: isolinderalactone, linderalactone, linderane, neolinderane and zeylanine (28),

the structure of which was determined by Joshi et al., in 1967 (38). The remaining five were named litsealactone (29), litseaculane (30), zaylanane (31), linderadine (32) and pseudoneolinderane (21) which was later also found in Lindera strychnifolia and has been previously mentioned. Takeda et al., determined the structures of litsealactone, litseaculane, and zeylanane in 1968 (39) and of pseudoneolinderane and linderadine in 1970 (40). Joshi et al., also isolated from Neolitsea zeylanica Merr. (38) zeylanidine (33) and zeylanicine (34).

Table 1. summarizes the occurrence of the 26 furanosesquiterpenes found in the Lauraceae family (41).

While the family Lauraceae, was being thoroughly examined by, for the most part, Takeda and his co-workers; the family, Compositae, was being examined with great thoroughness by Novotny, Sorm, Herout and others in Czechoslovakia.

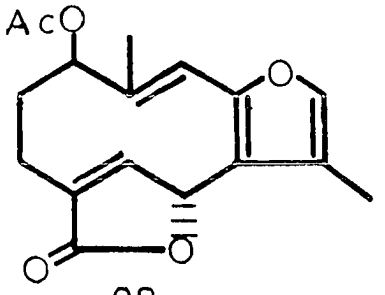
Persuing early work by Aebi et al., (42) and by Stoll et al., (43), Novotny and his collaborators (in 1962) undertook the investigation of the Czechoslovakian plants Petasites officinalis Moench., and Petasites albus (L) Gaertn.

From the first of these, Petasites officinalis, Novotny et al., (44) isolated from coltsfoot rhizomes: furanopetasin (35), furanoeremophilane (36), and furanoeremophilone (37). The same group of workers later described the structure

Table 1. The distribution of the Lauraceae furanosesquiterpenes.

| Sesquiterpene | Lindera strychnifolia | neolitsea sericea | neolitsea aciculata | neolitsea zeylanica |
|---|---|---|---|---|
| lindestrene | + | + | - | - |
| lindenenol | + | - | - | - |
| lindenenene | + | + | - | - |
| linderoxide | + | - | - | - |
| isolinderoxide | + | - | - | - |
| isofuranogermacrene | + | - | - | - |
| lindenenone | + | - | - | - |
| neolinderalactone | + | - | - | - |
| linderane | + | - | + | + |
| linderalactone | + | + | + | + |
| isolinderalactone | + | + | + | - |
| lindenenol acetate | + | - | - | - |
| pseudoneolinderane | + | - | + | - |
| epidihydrolinderalactone | + | - | - | - |
| neosericenyl acetate | + | - | - | - |
| sericenine | - | + | - | - |
| sericenic acid | - | + | - | - |
| isosericenine | - | + | - | - |
| neosericenine | - | + | - | - |
| litsealactone | - | - | + | - |
| litseaculane | - | - | + | - |
| linderadine | - | - | - | + |
| zeylanine | - | - | + | + |
| zeylanane | - | - | + | - |
| zeylanidine | - | - | - | + |
| zeylanicine | - | - | - | + |

proof of these compounds (45,46).



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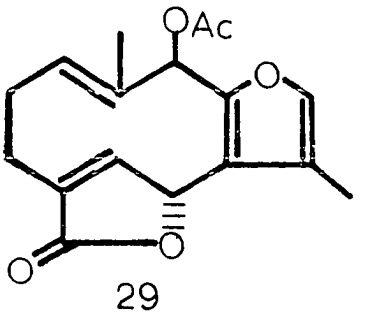

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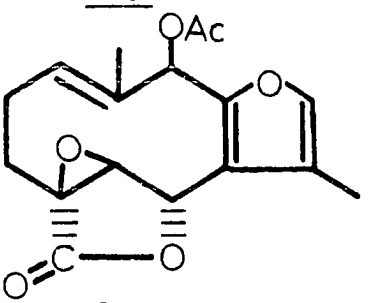

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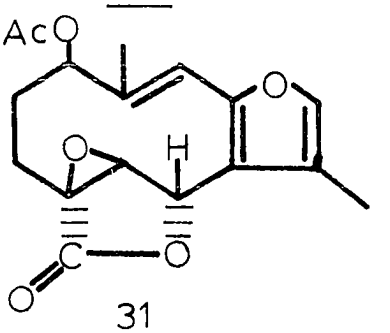

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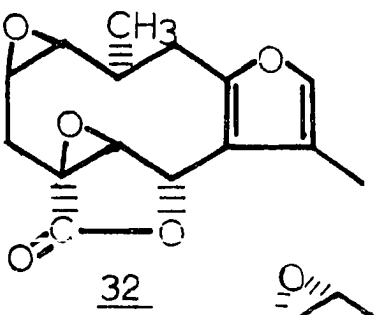

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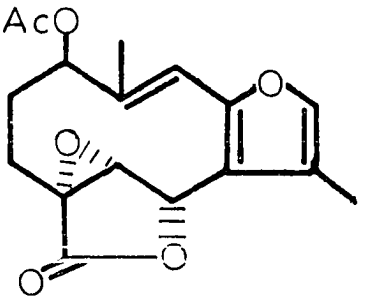

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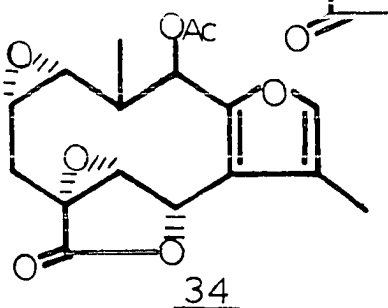
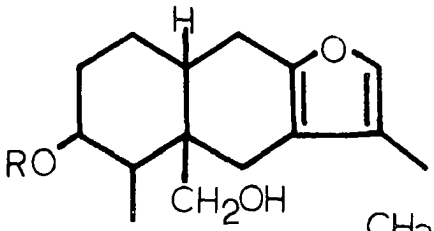


34

The closely related plant, Petasites albus (L) Gaertn, was examined by Novotny, Herout and Sorm in 1962 (47). Furanoeremophilane was again found but three new furan compounds were also isolated. The same group later deduced the

structures of two of these: petasalbin (38) and albopetasin (39), (48). The third, named albopetasol has been found to contain the furan ring and two hydroxyl groups, has been assigned probable structure 40, (49).

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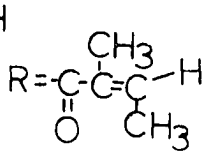
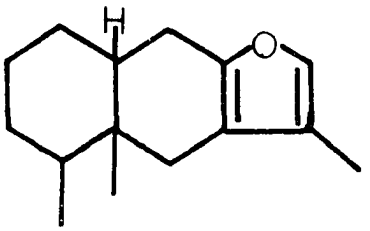



(Ang)

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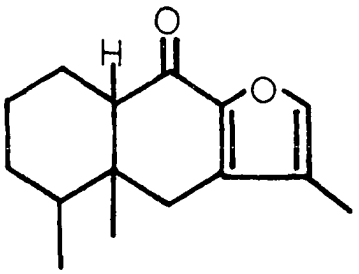


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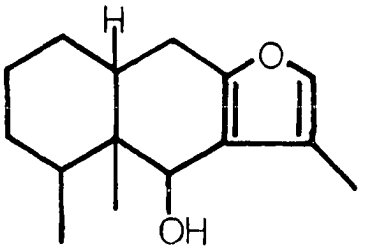


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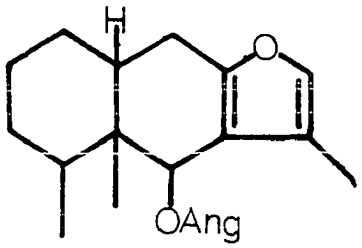


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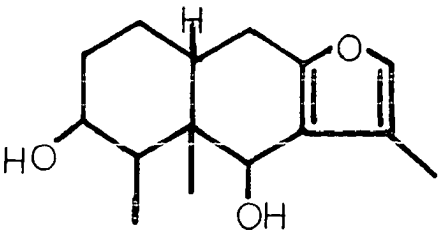
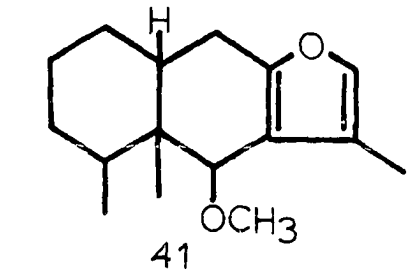



40

**Petasites spurius** (L) Achl., was found to contain albopetasin, petasalbin and furanoeremophilane and is therefore chemotaxonomically closely related to P. albus (50).

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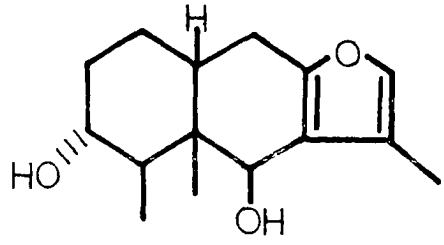


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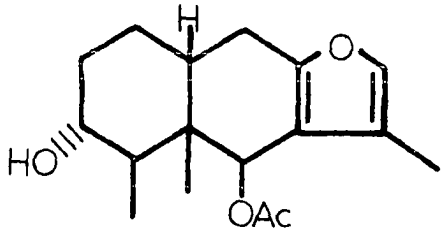


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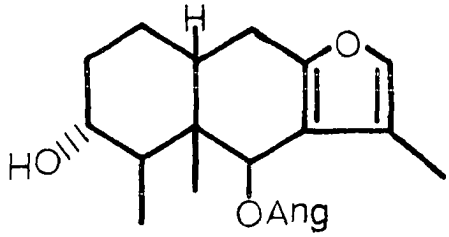


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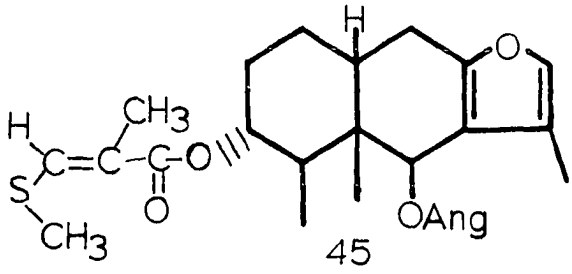


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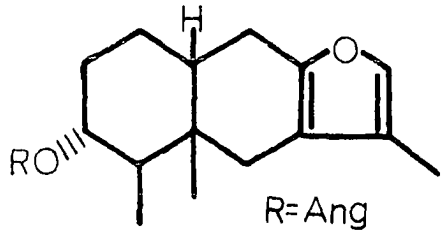



46

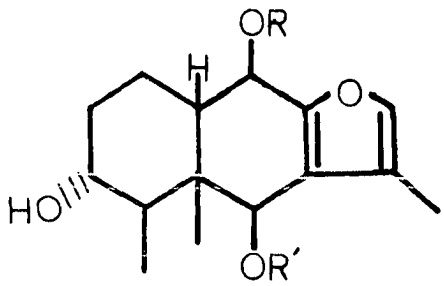
Concurrent with the above work, was the investigation of Petasites japonicus Maxim., undertaken by K. Naya et al., in Japan. Naya and his co-workers (51) isolated fifteen components from the rhizomes of P. japonicus; ten of these contained the furan ring. In addition to ligularenone (vide infra), furanoeremophilone, albopetasin and petasalbin, six new furanosesquiterpenes were obtained by gas phase and column chromatography. The new compounds have been named

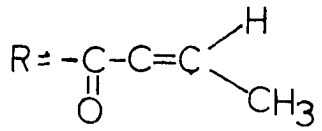
petasalbin methyl ether (41), furanofukinol (42), 6-acetylfuranofukinol (43), 6-angelylfuranofukinol (44), S-furanopetasitin (45) and furanojaponin (46).

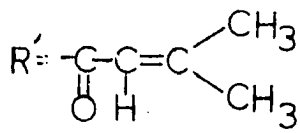
Two other members of the genus Petasites were recently investigated, Petasites kablikianus from which kablicin (47) was isolated and Petasites paradoxus which also contained kablicin with some of the sesquiterpenes found in P. albus (52).

Several other members of the Compositae family are currently under examination. Liguaria sibricia Cass., has been found to contain ligularone (48) and petasalbin and Ligularia fisheri has been found to contain furanoeremophilane; ligularone and petasalbin are also sometimes found in this plant (53,54). Patil et al., have isolated from "San-Shion", a Chinese drug made up of Ligularia, a new compound which they have named furanoligularenone (49), (55), while Takahashi has isolated the closely related 10-β-H-ligularenone (50) from Ligularia stenocephala (56). The only other Ligularia variety which has been examined is L. hodgsoni Hook, from which furanoeremophilane-14-β,6-α-olide (51) was isolated in 1969 (57).

Atractylon (52) was isolated from Atractylodes japonica Koidz. (Compositae) by S. Takagi in 1921 (58) and again in 1925 (59). It has also been found in Atractylodes chinesis Koidz. Its structure was determined recently by Hikino et

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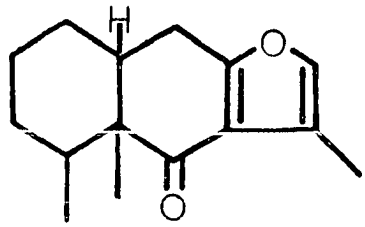


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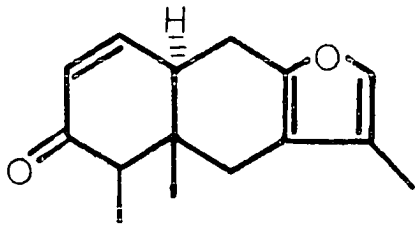


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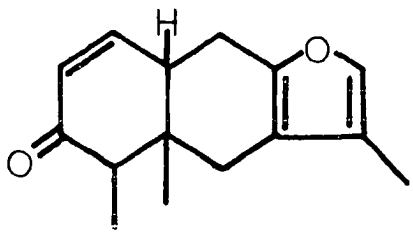


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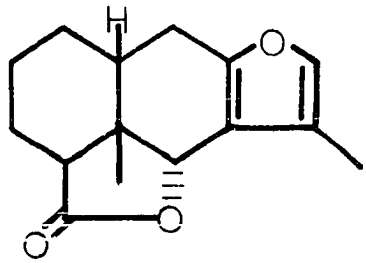
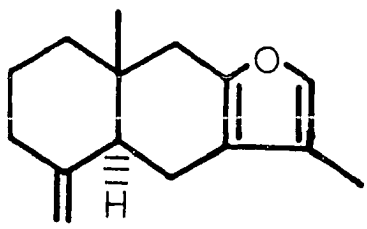



51

al., (60,61).

Adenostyles alliariae Kern (Compositae) has been found to contain three furanosesquiterpenes of the eremophilane type: adenostylone (53), isoadenostylone (54) (62), and neoadenostylone (55) (63). The first two of these contain unusual isobutyl ether functions (64).

A South African plant, Euryops floribundus, also a Compositae, was found to contain two eremophilane type furanosesquiterpenes. These are euryopsonol (56) isolated in 1954 (65) and identified in 1967 (66) and euryopsol (57) which was isolated and identified in 1969 by Eagle et al. (67). Bohlmann et al., (68) reported fourteen additional furanosesquiterpenes in 1972. These are 58-73 shown in Chart II.

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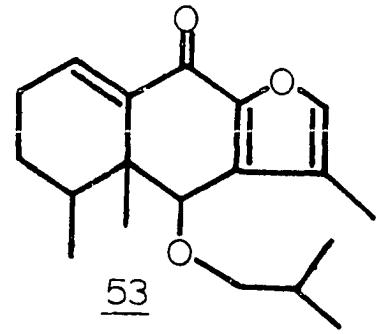


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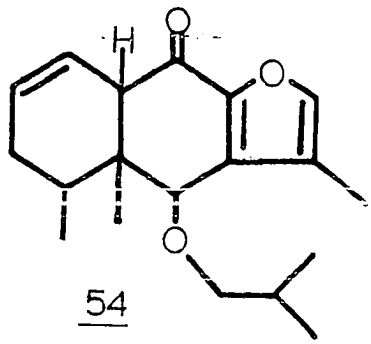


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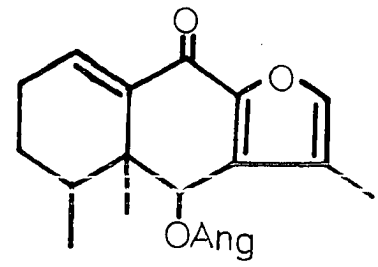


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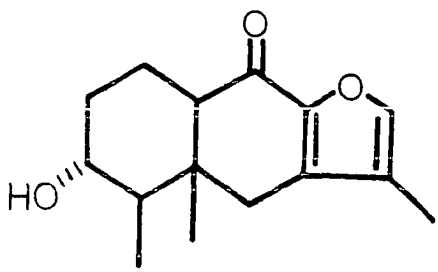


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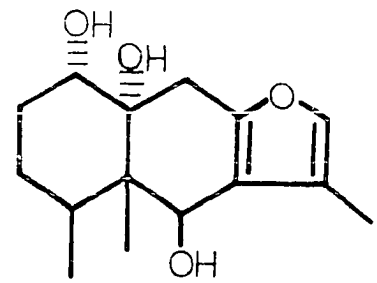
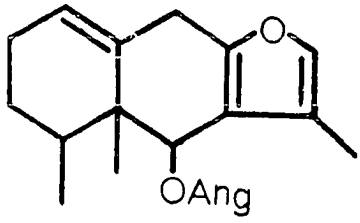



57

Chart II

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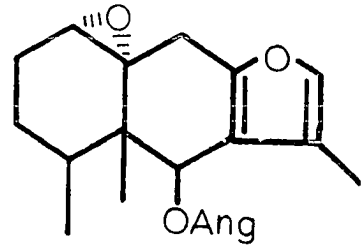


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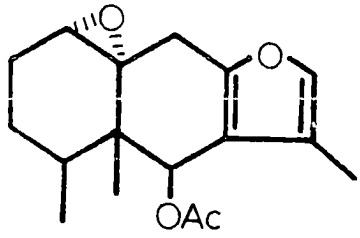


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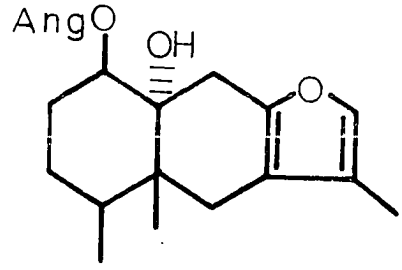


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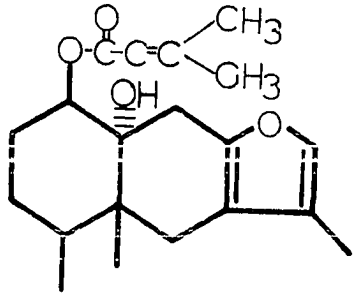


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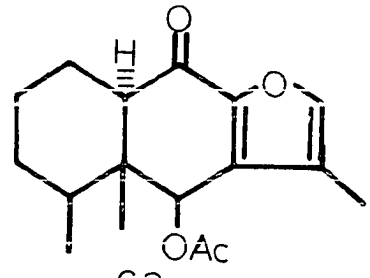


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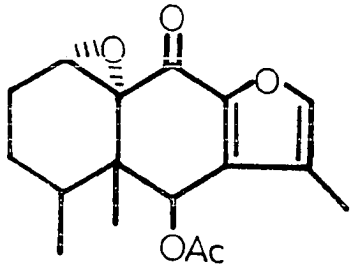


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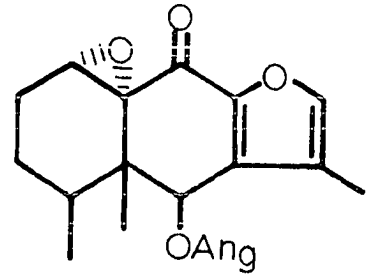
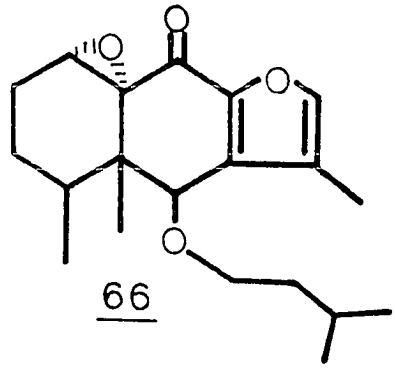



65

Chart II (Cont.)



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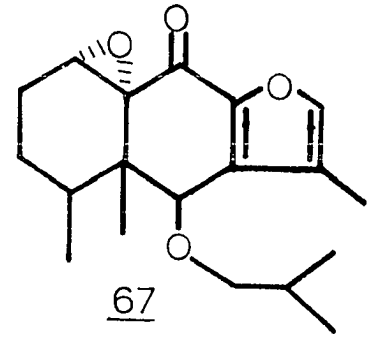

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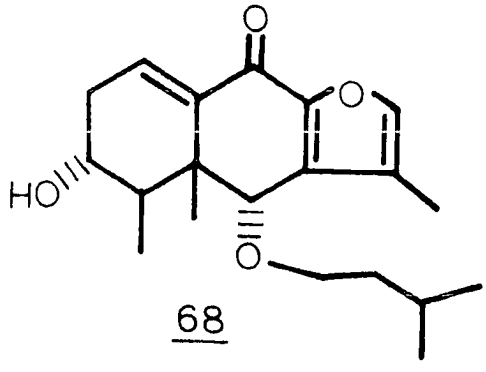

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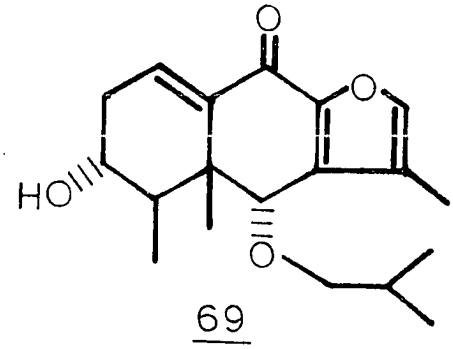

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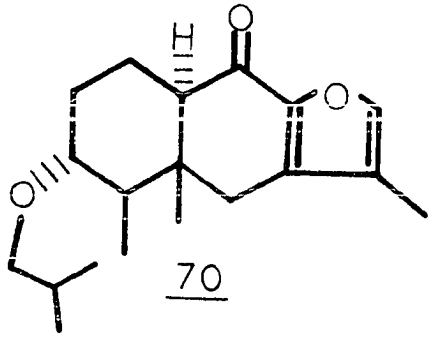

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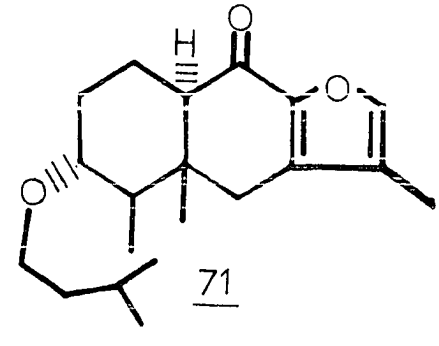

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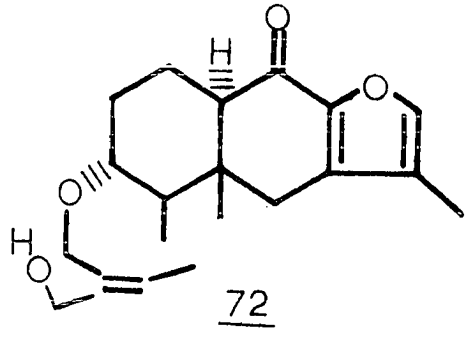

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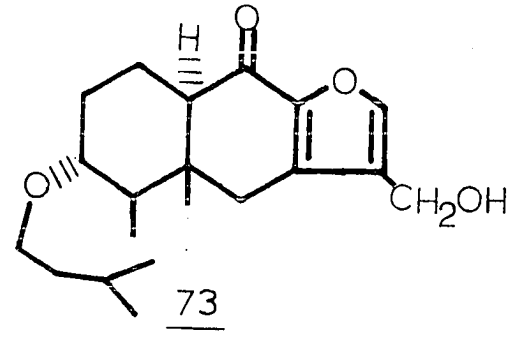
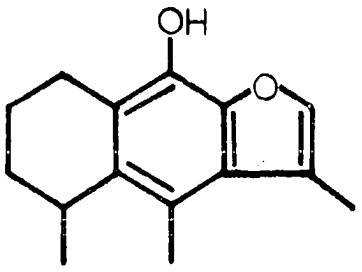


73

Cacalea decomposita A. Gray (Compositae) has been thoroughly examined by a group of researchers in Mexico headed by J. Romo. They isolated, in 1964, six furanosesquiterpenes which they named cacalol (74), cacalone (75), maturone (76), maturinin (77), maturinone (78), and maturin (79), (69,70). The structures of the first of these, cacalol and cacalone, were determined by Romo and Joseph-Nathan (69). Later Romo (71) revised the structure of cacalol to 80, and reported the isolation of decompositin (81). The structures of the remaining four compounds were finally correctly determined by Brown and Thomson in 1969 (72).

Finally, in the family Zingiberaceae, the rhizome of zedoary, Curcuma zedoaria Roscoe, has afforded seven new compounds: curzerenone (82), (73), epicurzerenone (83), (73), zedarone (84), (74), curcolone (85), (75), furanodienone (86), (76), isofuranodienone (87), (76), and furanodiene (88), which Hikino et al., (77), believe to be the biogenetic precursor of the others.

As is obvious by now, the decade between 1962 and 1972 has seen the emergence of the furanosesquiterpenes as a large and ubiquitous class of compounds. Before 1962 only two furanosesquiterpenes were known, atractylon (52) and lindenenol (9); today there are well over eighty with more being isolated every year. This manuscript is concerned with

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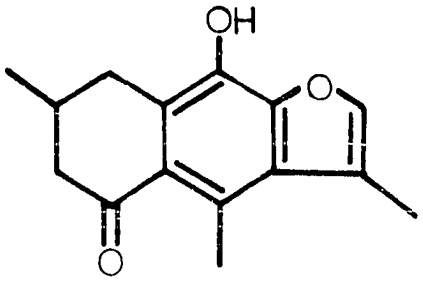


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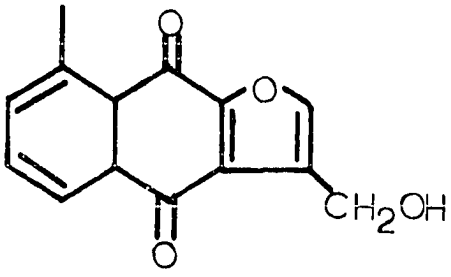


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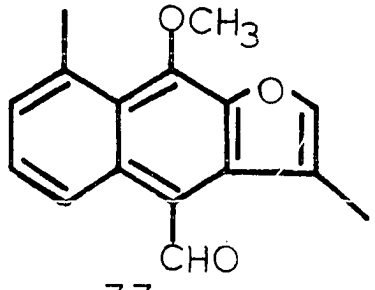


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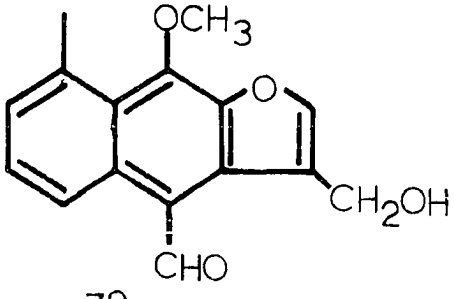


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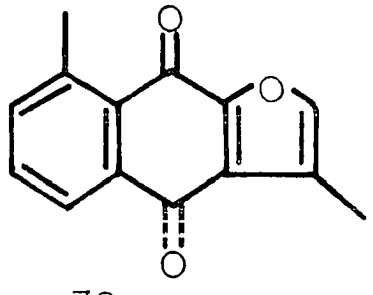


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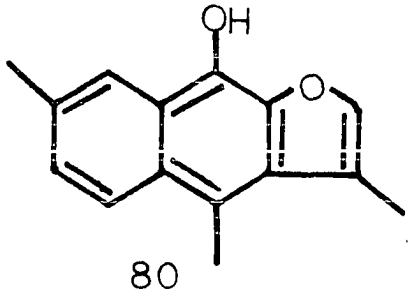


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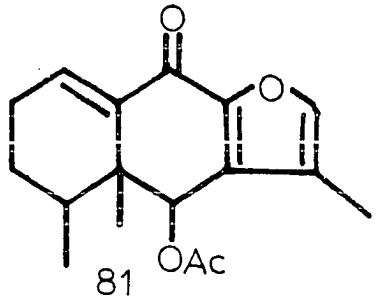


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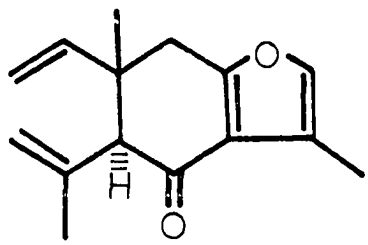

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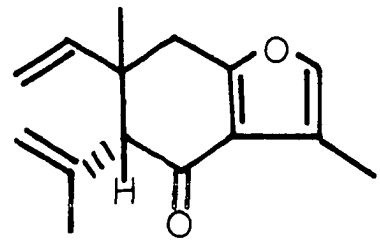

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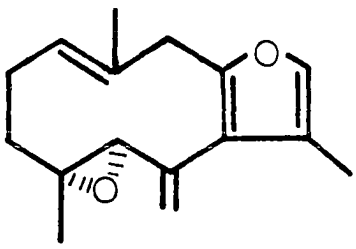

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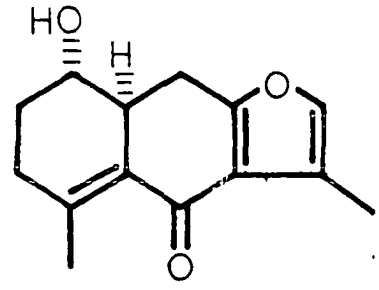

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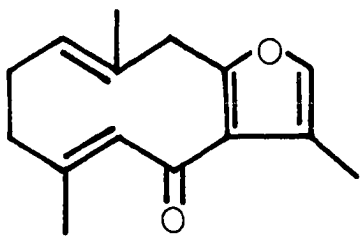

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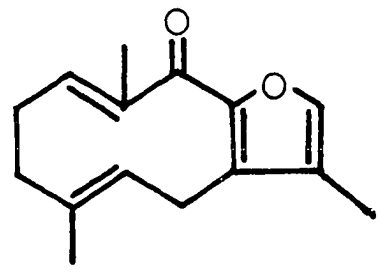

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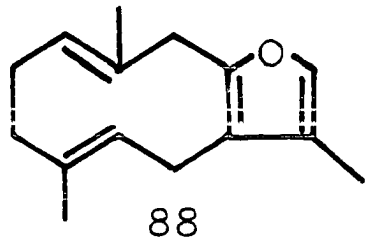


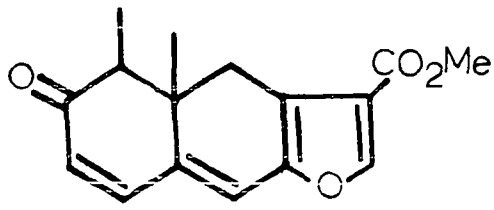
88

the synthetic approaches to yet another furanosesquiterpene, warburgin (89).

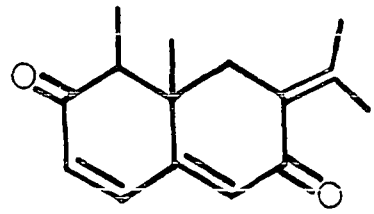
The genus Warburgia is a class of the small and widely distributed family Canellaceae, which in turn is a division of the phytogenetically ancient group of woody plants of the order Magnoliales. The tree, Warburgia ugandensis Sprague,

from whose heartwood warburgin is isolated, often grows to 90 feet and, in Uganda, trees as tall as 140 feet are not uncommon. Warburgia ugandensis or East African Greenheart, is an important timber tree whose wood resembles teak in its satiny luster. When freshly cut the wood has a fragrant incense-like odor closely resembling sandlewood and, in fact, Greenheart wood has been sold as sandalwood in Zanzibar! The bark of this tree has been used as a purgative and its resin has been used by the natives to fix tools in handles. Also, the oil of the closely related W. breyeri Pott., has been used as a remedy for low fever (78).

When Brooks and Draffan reported the isolation of warburgin and warburgadione in 1966 (13), they were able to propose the tentative structure (89) for warburgin. Their definitive publication (79) appeared in 1969 in which they confirmed structures 89 for warburgin as well as structure 90 for warburgadione.



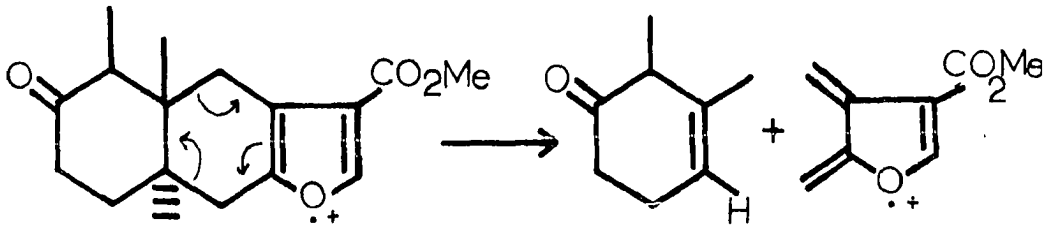

89




90

Warburgin was isolated from fractions eluted by benzene in the chromatography of the heartwood petroleum ether extract. The compound crystallizes as pale yellow prisms which melted at 159-161°. Elemental analysis indicated the formula to be $C_{16}H_{16}O_4$. A band in the infrared spectrum at 1679 $cm^{-1}$ indicated a conjugated ketone; while a band at 1734 $cm^{-1}$ indicated the presence of an ester function. The presence of a methyl ester was confirmed by the nuclear magnetic resonance spectrum which shows a peak at 6.10 τ and by chemical evidence: alkaline hydrolysis followed by methylation regenerated warburgin. The final oxygen was accommodated in a furan ring, evidence coming from ir bands at 3156 and 1566 $cm^{-1}$.

Catalytic hydrogenation of warburgin yielded a compound of the formula $C_{16}$ $H_{20}$ $O_4$ with the uptake of two moles of hydrogen. The ir spectrum of this compound confirmed that the furan and the ester moieties remained unchanged, however the ketone absorption was shifted to 1721 $cm^{-1}$ (saturated ketone). Evidence supporting placement of the carbomethoxyl function on the 3-position of the furan ring came from the nmr absorption of the furano hydrogen (deshielded) as well as the base peak in the spectrum at m/e 152, which is considered to arise from "retro-Diels-Alder" cleavage as depicted 91 92 below.

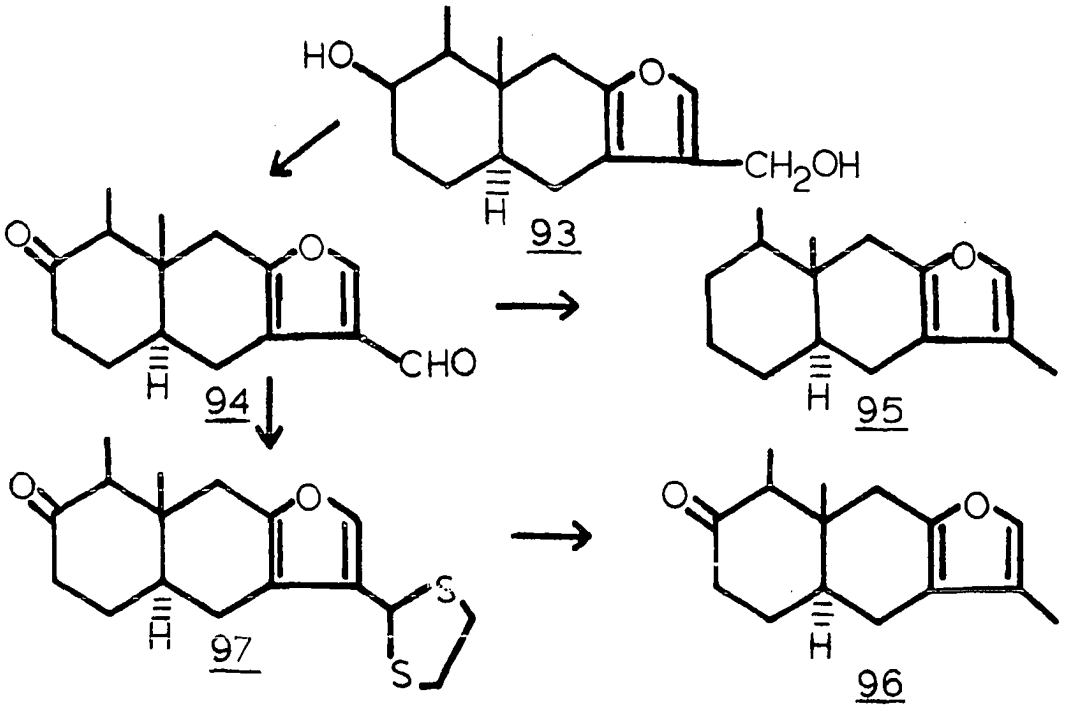


91 92

The physical and chemical data presented above described by Brooks and Draffan (79) suggested the structure warburgin (89). To confirm this structure, Brooks and Draffan reduced tetrahydrowarburgin with lithium aluminum hydride to give diol 93. Oxidation of this compound with chromium trioxide in pyridine yielded ketoaldehyde 94, which they then reduced (Huang-Minlon) to furanohydrocarbon 95. This compound proved to be similar to authentic cis-furanoeremophilane but distinguishable by GLC. This evidence strongly suggested a trans ring fusion in 93, 94, and 95.

Final proof was supplied by a direct correlation of ketoaldehyde 94 with the known furanoligularone 96 [the dihydro-derivative of furanoligularenone (49)]. Ketoaldehyde (94) was treated with ethanedithiol giving the thioacetal (97) which in turn was treated with Raney nickel in dioxane affording a compound identical with furanoligularenone (96).

The above evidence confirmed the gross structure of warburgin as depicted in structure 89. The stereochemistry

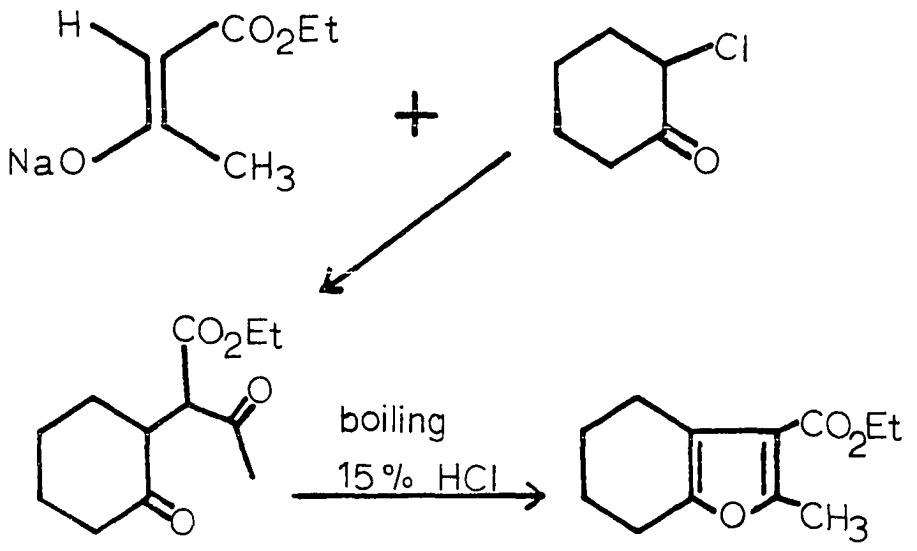



of the C-4 and C-5 methyl groups remained to be determined but Brooks and Draffan (79) present convincing evidence based on an ORD comparison between the known compounds eremophilone and nootkatone. Nootkatone has stereochemistry opposite that of eremophilone. Comparison of the data on Cotton effect curves due to the carbonyl chromaphore in warburgin with that for authentic furanoliqularanone demonstrates the stereochemistry of warburgin as 89.

No reports are available in the literature concerning the biogenetic precursors of warburgin.

Few attempts have been made at synthesizing furanosesquiterpenes. The difficulty arises in building the 3-substituted furan moiety. Lednicer and Emmert (80) have introduced a furan ring into steroids as the "A" ring but have not sub-

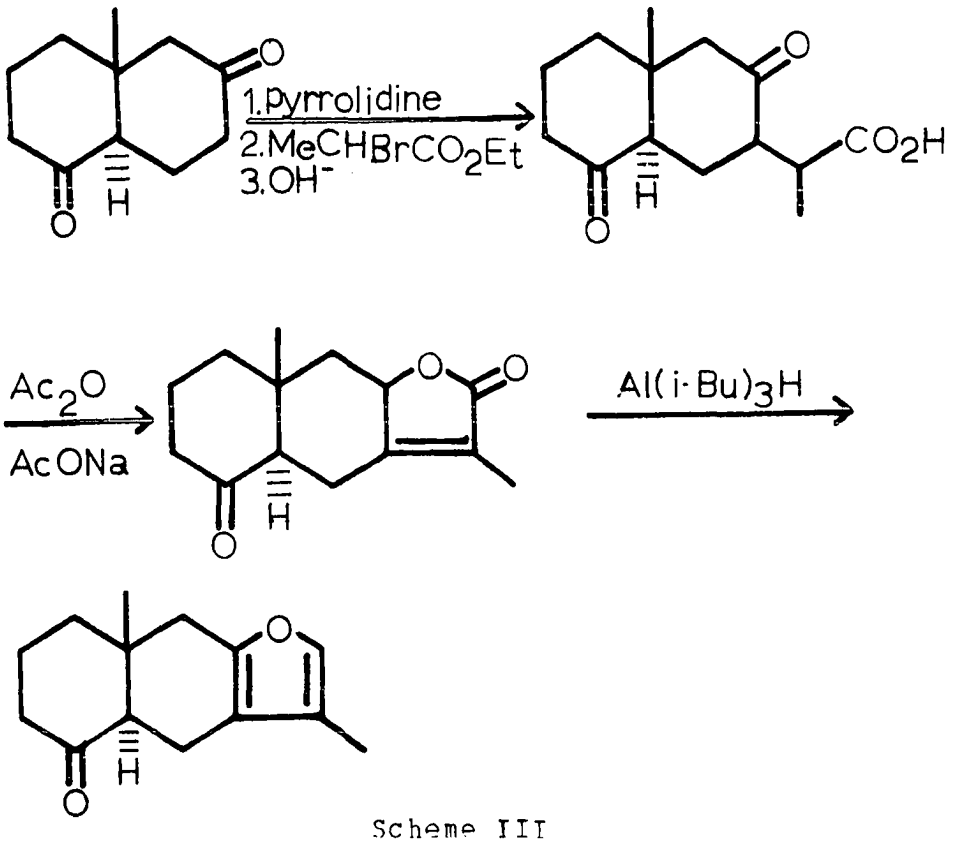
stituted the furan in either the 2 or 3 position. Ebel et al., (81) have synthesized the 2,3 disubstituted compound as shown below; however, to date no 2,3 disubstituted furanosesquiterpenes have been found.



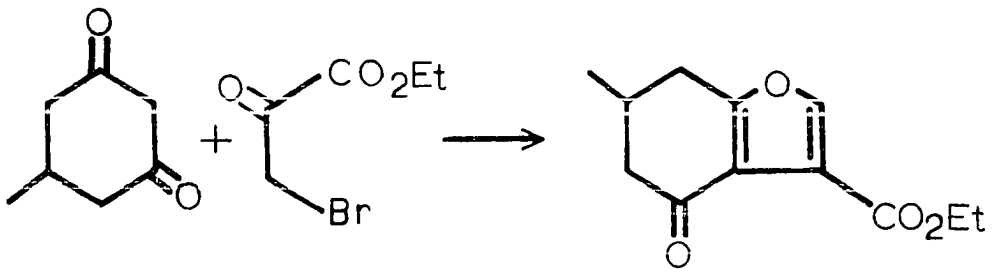

Minato and Naqasaki have developed a method for the synthesis of 3-methyl furans which they have put to use in the synthesis of atractylon as shown in Scheme II below (82).

Finally Stettler and Lauterback (83) have been able to synthesize a furan compound which has oxygen functionality in the 3 position (Scheme III). However this method is useful only for symmetrical diones which greatly limits its utility.

Scheme II



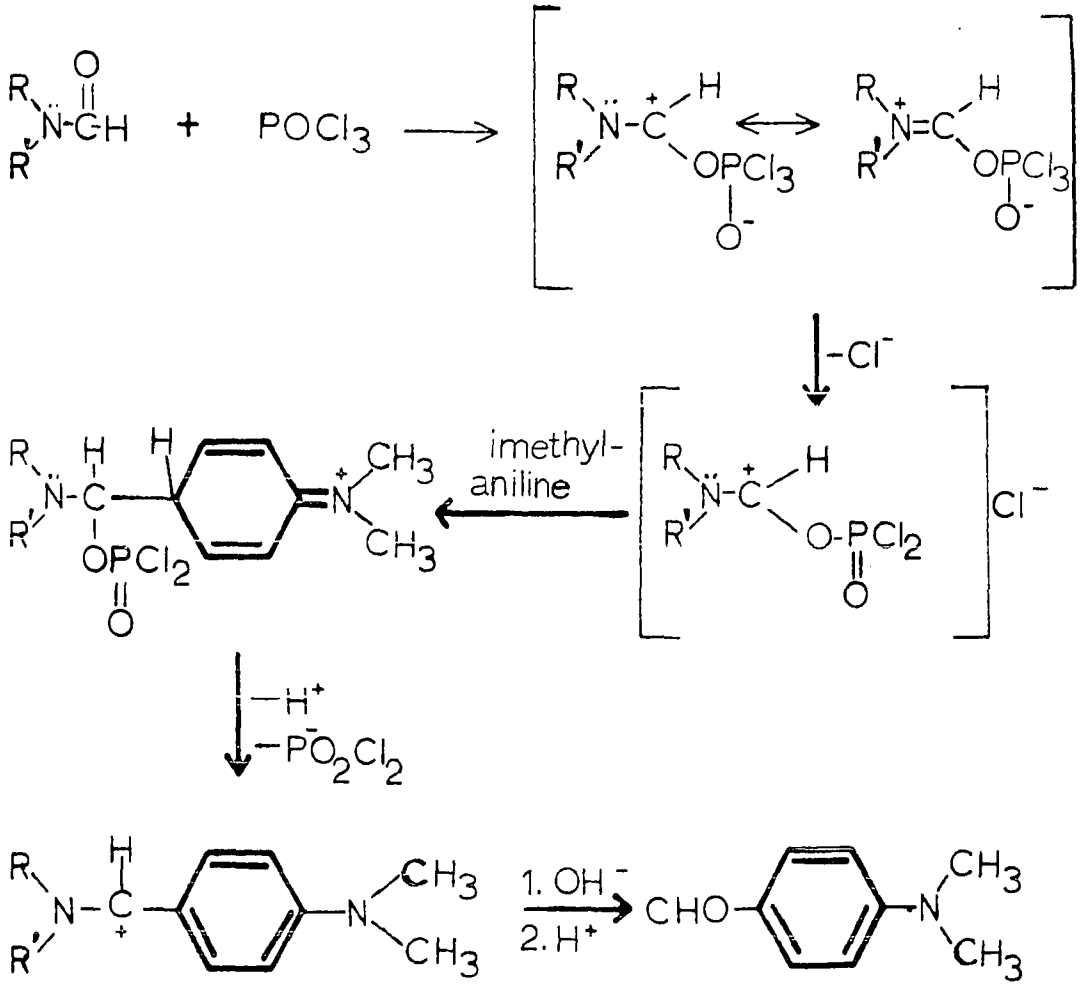

Scheme III



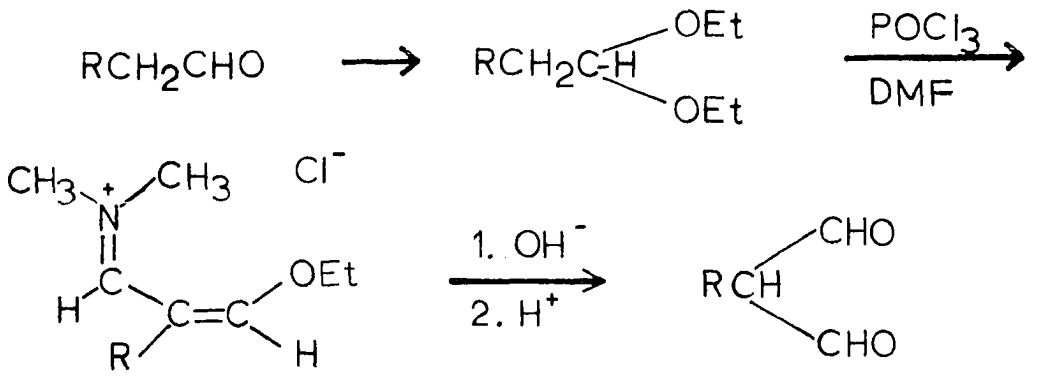

The Vilsmeier Reaction

One of the most important classes of reactions in organic synthesis is alkylation on carbon. By means of alkylations the skeleton of a desired compound can be built up from large fragments. There are many types of alkylating

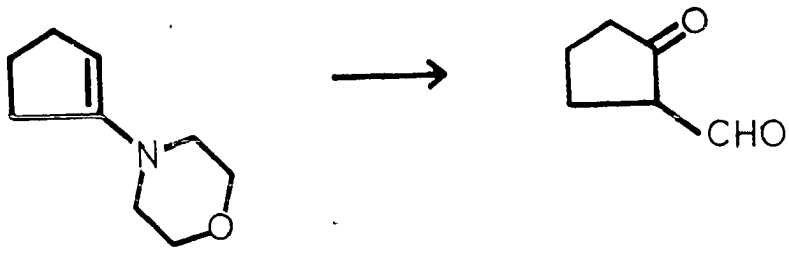
agents, diethyl- and dimethylsulfate, Meerwein's reagent, methyl vinyl ketone, alkyl halides and aryl halides just to name a few. Each of these reagents is useful under certain conditions. The Vilsmeier reagent, a 1:1 complex of a substituted formamide (usually dimethylformamide) with phosphoryl chloride or phosgene, has been used extensively to alkylate aromatic compounds, usually giving the corresponding aldehyde (84). A typical reaction of this nature is shown below. A very thorough review of this reaction was published in 1962 (85).

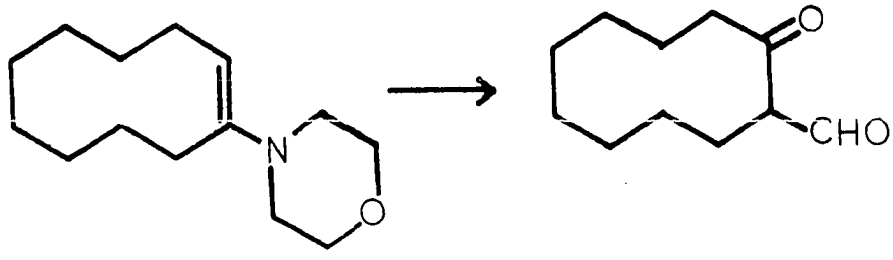


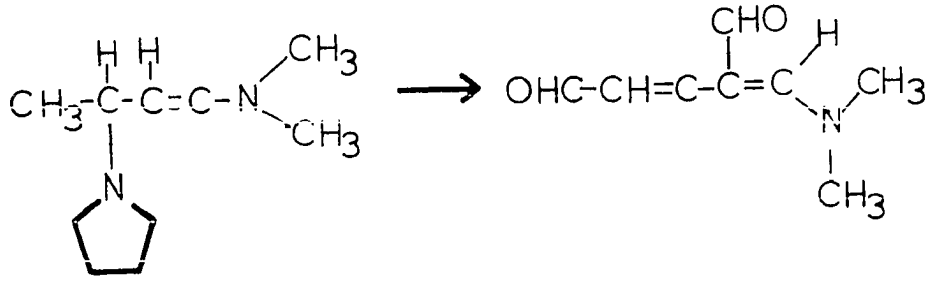
In 1957 , Arnold and Sorm (86), extended the use of the Vilsmeier reagent to the alkylation of aliphatic compounds having active hydrogen, notably to the diethylacetals of aliphatic aldehydes. They further developed this work in 1958 (87) and used the reaction in the preparation of β-dialdehydes, by the reaction shown below.




The application of the Vilsmeier reagent to ketomethylene systems was studied by Arnold and Zemlicka (88); Burn and his co-workers have used it to introduce a carbon substituent at C-6 in the steroid molecule (89). Arnold reported the first use of the Vilsmeier reagent with an enamine in 1959 (90), and Ziegenbein again in 1965 (91). Examples of this are shown below. It is a variation of this reaction which we hoped to use as the key step in our synthesis.


N
O
O
CHO


N
O
O
CHO

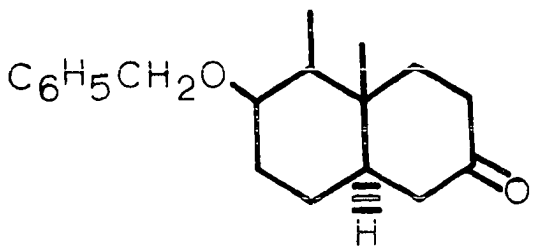

H H
CH3
CH3-C-C=C-N
CH3
N
CHO
H
OHC-CH=C-C=C
CH3
N
CH3

# DISCUSSION

## Introduction

The synthesis of warburgin presents two major problems; first, the development of a series of reactions which would allow the preparation of a 3-oxo substituted furan ring; second, the synthesis of suitably substituted decalin ring system which could ultimately be transformed to warburgin after the introduction of the furan ring.

We approached the first problem by trying to develop ways by which cyclohexanone, a presumably good model compound, could be annulated to the desired 3-oxo substituted furan. Upon the successful completion of the model studies, work was begun on the synthesis of the necessary intermediate which could hopefully be transformed to warburgin. This intermediate was trans-3,4,4a,5,6,7,8,8a-octahydro-r-4a-c-5-dimethyl-6-benzyloxy-2(1H)-naphthalenone (98).




98

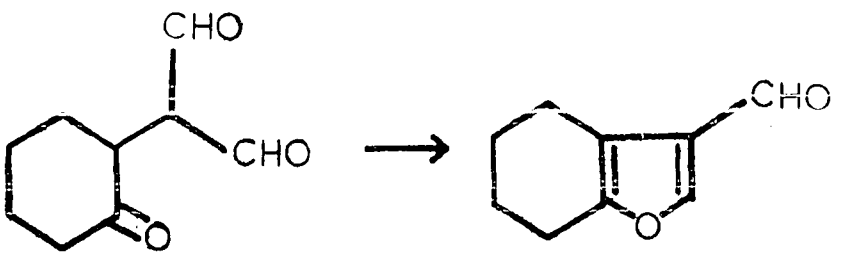
The approaches to the synthesis of ketone 98 comprise the second part of this section. The final part of this section

is concerned with the attempts to convert intermediate 98 to warburgin itself.

## Model Studies

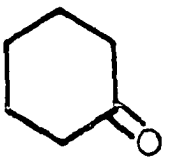
Since we eventually hoped to convert intermediate 98 to warburgin we chose, as a starting material for our model studies, cyclohexanone. Like 98, cyclohexanone contains an alicyclic ketone and therefore it was hoped that it would parallel the reactions of the more complicated starting material to be used later.

The method we had chosen to employ involved the cyclization of a suitably substituted γ-keto aldehyde, such as, 99 which might be expected to readily cyclize to the furancarboxaldehyde 100.




99 100

The work of Stork et al., (92) which has been reviewed by Szmuszkovicz (93), provided a facile route to the system we desired. The two step enamine alkylation with ethyl bromoacetate shown below (101-103) gave crude ethyl 2-cyclohexanoneacetate in 65% yield.



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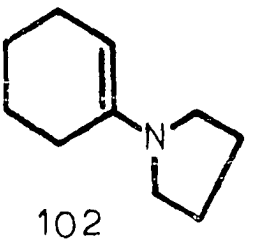

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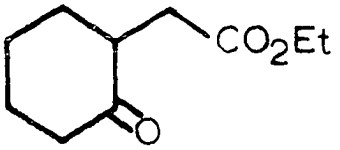

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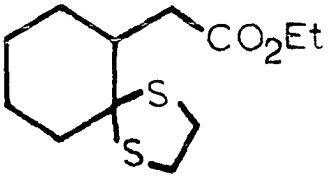

104

After distillation, keto ester 103 was treated with slightly more than one equivalent of ethanedithiol (94) giving thioacetal (104) in 80% yield. Originally, use of the more readily removable ethylenedioxy protecting group was investigated.[1] Unfortunately, later work showed that this group was incompatible with subsequent transformations.

It was necessary at this point to convert ester 104 to the aldehyde (105).

Since a second functional group had to be introduced in order to obtain β-dialdehyde 99, a few words as to why 99 was chosen are in order.

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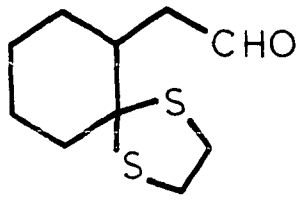
[1]Preparation of these compounds is given in the experimental section.

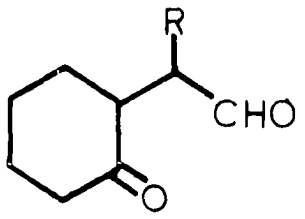



105

The synthesis of furan or substituted furans from 1,4-dicarbonyl compounds [the Paar-Knorr syntheses (95,96)] is the oldest known method for their preparation. Normally, heating with a dehydrating agent is sufficient to effect cyclization.

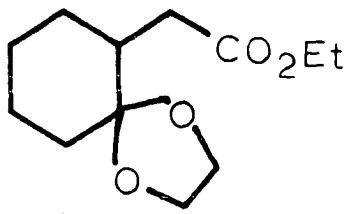
For our own purposes a compound similar to 106 should cyclize readily. The "R" group, however, must be suitably designed to be readily converted into the methyl ester found in warburgin. Accordingly, since a compound similar to 104 was available, it would seem that introduction of a hydroxymethylene group $\alpha$ to the ester should provide an entry into the desired furan system. Unfortunately, when the conversion 107-108 was attempted, only starting material was obtained.

Another reaction, 102-109, was also attempted but cyclohexanone was the only product isolated (97).




106

R = $CH_2OH$
= CHO
= $CO_2Et$
= $CO_2H$

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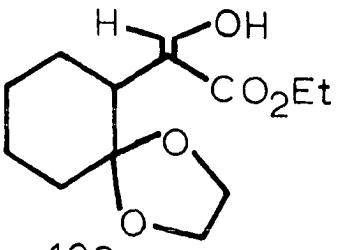
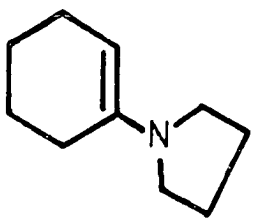
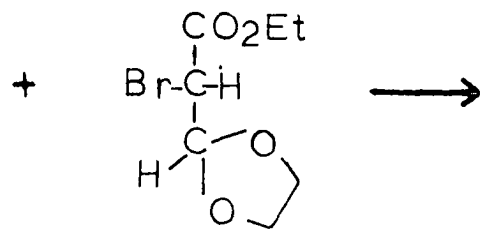
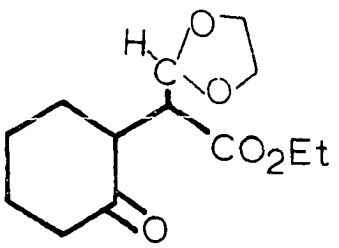



108




102

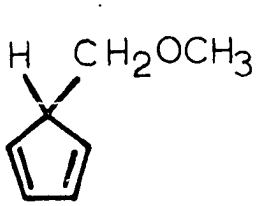


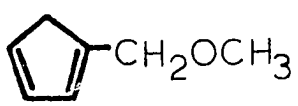

109

Direct alkylation of thallium cyclopentadienide with 2-bromocyclohexanone was also investigated. Corey has recently shown that, under carefully controlled conditions,

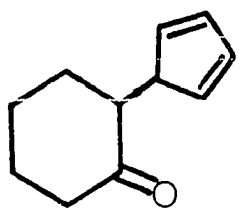
adduct 110 is favored over adduct 111 when thallium cyclopentadienide is alkylated with chloromethyl methyl ether (98). The desired 1-(2-oxocyclohexyl)cyclopentadiene (112) might well have been readily cleaved with ozone to the β-dialdehyde 99. However, compound 112 failed to form. It is probable that 2-bromocyclohexanone is simply not active enough as an alkylating agent.




110

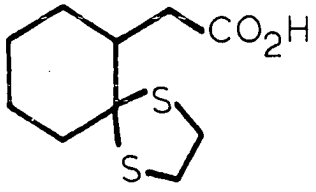



111

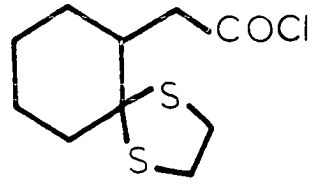



112

Thus we came to consider the treatment of a derivative of 105 with the Vilsmeier reagent. In order to obtain aldehyde 105 from thioketal ester 104 two approaches were possible. The first of these, reduction to the aldehyde, can be accomplished in several ways. The ester could be hydrolyzed to the acid 113 which could then be converted to the acid chloride 114 and treated with hydrogen and a suitable catalyst such as palladium on barium sulfate [Rosenmund reduction (99)]. Since this is tedious and often poorly reproducible, one of H. C. Brown's reducing agents was employed instead.




113




114

The thioketal ester (104) was converted to the acid (113) and this in turn was converted to the acid chloride (114) with oxalyl chloride and sodium hydride. The acid chloride was then treated with one equivalent of lithium tri-t-butoxyaluminum hydride at -78° in diglyme; a reaction developed by Brown and Rao (100). Although this reaction did lead to the aldehyde, the yields (15-25%) were consistently low.

In a related reaction (101), the thioketal ester (104) was treated with sodium bis(2-methoxy)aluminum hydride (Vitride[1]) at -70°. Repeated attempts failed to give the desired aldehyde in yields greater than 25-40%.

Alkylation of cyclohexanone enamine (102) or of cyclohexanone (in the presence of sodium hydride) with the diethyl acetal of bromoacetaldehyde, failed to yield

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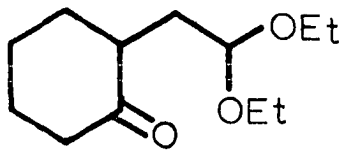
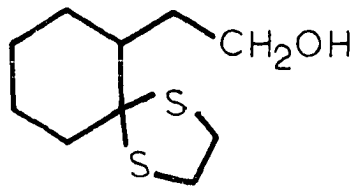
[1]Eastman trademark.

appreciable amounts of the desired aldehyde precursor 115.




115




116

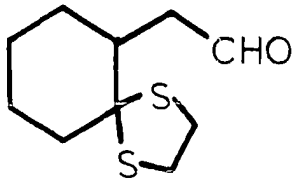
The second route investigated was the reduction of thioketal ester 106 to the alcohol 116 and subsequent mild oxidation of the alcohol to the aldehyde. The reduction was accomplished utilizing an ethereal solution of lithium aluminum hydride at reflux. Yields initially ranged from 80-85% but subsequent experiments showed that a virtually quantitative yield could be obtained if tetrahydrofuran was used as the solvent. This effect is probably due to the higher reflux temperature attainable with tetrahydrofuran and to the fact that ester (104) is far more soluble in tetrahydrofuran than in ethyl ether.

The oxidation of alcohol 116 to the aldehyde was the next problem to be dealt with. Many reagents have been used to oxidize primary alcohols to aldehydes. Our initial choice was the Collins' reagent (102). This reagent (the dipyridine complex of chromic anhydride) with dichloromethane as solvent, has several good features. The complex is readily

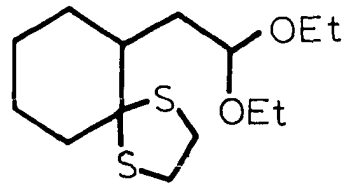
prepared (103), stable if dry, easily handled, and readily soluble in dichloromethane. Also, the reaction is run at room temperature lessening the chances of side reactions such as over oxidation. The procedure does have the drawback that the reaction itself generates large quantities of acidic residues and the isolation of the product from these residues is tedious, particularly on a modest to large scale oxidation. Using a modification of the procedure of Dauben et al., (103), we were able to obtain the aldehyde in yields of 60-65%. At a later stage of our investigations, we performed the oxidation using a pyridine-sulfur trioxide complex in dimethylsulfoxide (104) raising our yields to about 85%. This reagent gave a much cleaner product once the proper conditions were discovered. The aldehyde was purified by formation of the bisulfite addition product which was thoroughly washed with ether and then decomposed with dilute sulfuric acid. The aldehyde regenerated in this fashion was of better than 95% purity.

As it originally appeared in the literature, the Vilsmeier reaction required the treatment of the diethyl acetal of an aldehyde with phosphorous oxychloride and dimethyl formamide. Consequently, the aldehyde (105) was converted to its diethyl acetal 117.

When the diethyl acetal was subjected to Vilsmeier conditions, the only identifiable product was aldehyde (105).




105



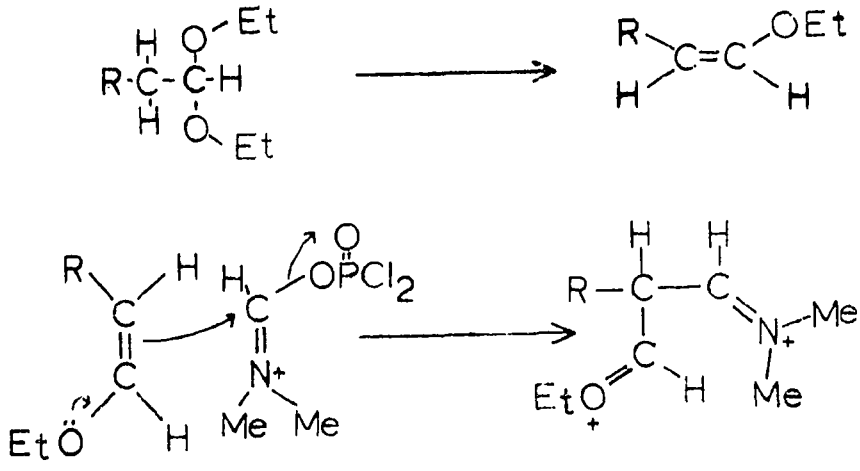

117

Repeated attempts over a large range of reaction times and temperatures failed to yield any dialdehyde.

At this point, we began to look into possible variations of the Vilsmeier reaction in considerable detail. Arnold (105) regards the Vilsmeier reagent as a cationic species which is readily attacked by an electron-rich source. In this case the diacetal is thought (86) to eliminate a molecule of ethyl alcohol and form a vinyl ether, which then can act as an electron source as shown below.

Since compound 117 is not reactive towards the Vilsmeier reagent under conditions reported in the literature, variations in experimental conditions were investigated on the more readily accessible n-hexaldehyde diethyl acetal. Low yields (15-20%) were obtained using a wide variety of conditions. Therefore, we decided to change reagents by using the enamine of the aldehyde rather that the diethyl acetal.

The reactions of enamines with the Vilsmeier reagent have received some brief attention in the literature (90,91)

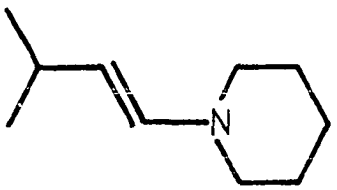


however enamines have not been used in the preparation of β-dialdehydes.

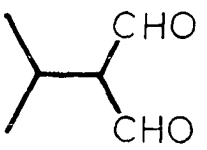
The pyrrolidine, morpholine and piperidine enamines of isovaleraldehyde were prepared (92) and each was treated with the Vilsmeier reagent. The conversion of the piperidine enamine (118) to the dialdehyde (119) was accomplished in approximately 70% overall yield.

In the course of our work we tried using both the DMF–$POCl_3$ and the DMF–phosgene Vilsmeier reagents but found little difference between them. We did observe that a much larger excess of Vilsmeier reagent to enamine was required for best yields.

Having determined satisfactory conditions for the Vilsmeier reaction on isovaleraldehyde, we returned to the



118

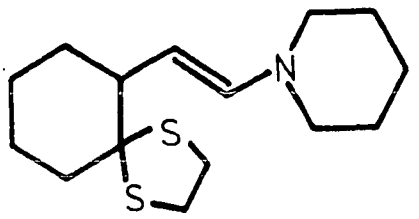



119

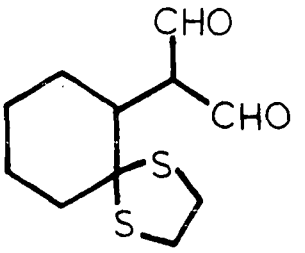
piperidine enamine (120) of thioketal aldehyde (105), and were able to obtain mediocre yields (7-40%) of dialdehyde. The best yields were obtained when rather long reflux times and high temperatures were used. Although the normal solvent for this reaction is a mixture of excess dimethyl formamide and ethylene dichloride, we attempted the reaction using many other solvents as well. None of these increased the yield. In fact, the less polar solvents decreased significantly the amount of product obtained. The piperidine enamine gave consistently better yields than the morpholine or pyrrolidine compounds.

Having obtained the dialdehyde (121) albeit in disappointing yield, it now remained to remove the thioketal blocking group and cyclize the keto dialdehyde (99) to a substituted furan (100).

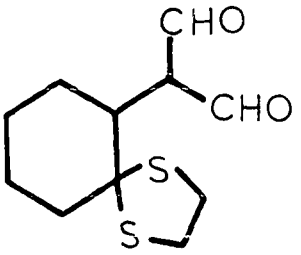
The usual method for removing a thioketal protecting group is described by Polini (106), utilizing mercuric acetate, water and acetic acid. However this method, in our



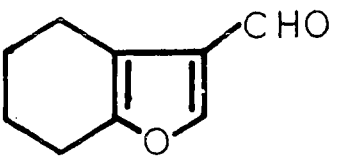
120



121



99



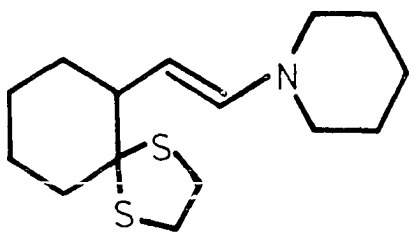
100

case, led to unidentified material and unchanged starting material. Corey and Erickson (107) have briefly reviewed other methods and also examined the known (108) cleavage of thioketals with mercuric chloride and calcium carbonate using acetonitrile instead of alcohol as solvent. The calcium carbonate is utilized as a base to neutralize the hydrochloric acid formed during the hydrolysis (107,109). Using this procedure we were pleasantly surprised to find not only cleavage of the thioketal but also cyclization of the resulting keto dialdehyde to the desired furan aldehyde (100). The yield of 89 based on dialdehyde 110 was 60-80% depending upon reaction time (see experimental).

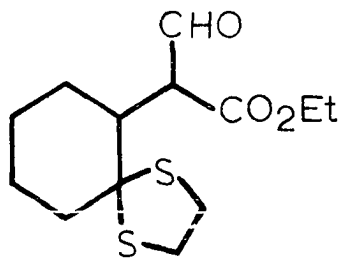
The crude furan aldehyde (100) was purified by column chromatography and identified by nmr, ir and high resolution

mass spectroscopy. In addition, the 2,4-dinitrophenylhydrazone was prepared and purified by repeated recrystallizations until its melting point was a constant 155-156.5°. Analysis of this compound for carbon, hydrogen and nitrogen was consistent with the proposed formula.

We had now accomplished our first objective in showing that the desired furan ring could be introduced into a cyclohexanone ring. However, since the overall yield was low we decided to try a possible alternative to the Vilsmeier reaction. This involved treatment of the enamine 120 with ethylchloroformate (92) with the hope of obtaining aldehyde ester 122.




120

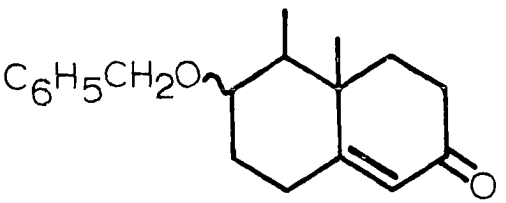



122

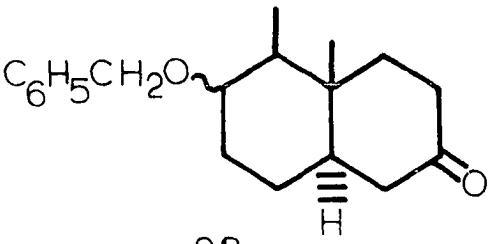
However since several attempts at this reaction gave only unchanged starting material, it was decided to proceed to the synthesis of the key intermediate in the warburgin synthesis: trans-3,4,4a,5,6,7,8,8a-octahydro-r-4a-c-5-dimethyl-6-benzyloxy-2(1H)-naphthalenone (98).

## Approaches to the Synthesis of trans-3,4,4a,5,6,7,8,8a-octahydro-r-4a-c-5-dimethyl-6-benzyloxy-2(1H)naphthalenone

Our initial plan of attack upon the synthesis of intermediate 98 was a modification of the work of Ken Burow in these laboratories (110). In the course of his synthesis of isopetasin, Burow synthesized a compound, 6-benzyloxy-4,4a,5,6,7,8-hexahydro-4a,5-dimethyl-2(3H)naphthalenone (123) which we hoped to convert, by reduction, to intermediate 98.



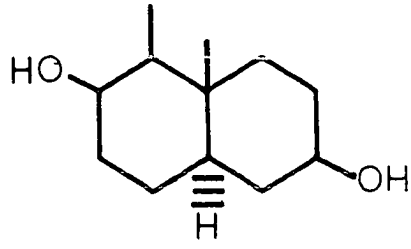

123




98

Since we needed the trans ring fusion to direct (111) the subsequent alkylation, we used the Birch reduction to effect this transformation (112). These conditions are also known (113) to remove the benzyloxy protecting group in the 6-position and therefore generate keto alcohol (124), which in turn would have to be reprotected. However several additional problems complicated the procedure.

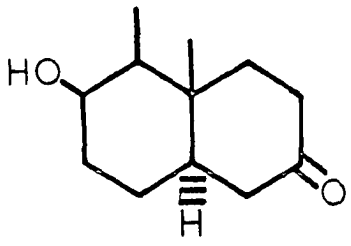
After synthesizing octalone 123 we subjected it to Birch conditions and instead of the expected keto alcohol (124) we obtained the diol (125) as the major product.



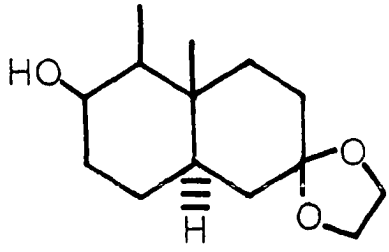

125

It became necessary to use a rather roundabout method to get to 98. The use of absolutely anhydrous ammonia (distilled from sodium) enabled us to reduce the octalone 123 to a mixture of keto alcohol 124 and diol 125. These were separated by column chromatography and found to consist of 70% keto alcohol by integration of the nmr spectrum. The keto alcohol was treated with ethylene glycol and p-toluenesulfonic acid to generate ketal-alcohol 126, which was then treated with excess benzyl chloride and sodium hydride to generate benzyloxy ketal 127. This compound was then treated with acetone and hydrochloric acid, cleaving the ketal and generating the desired benzyloxy ketone 98.

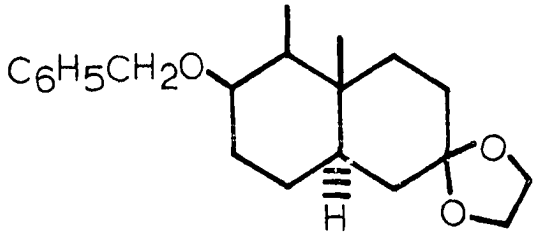
The overall yield of this process, based on octalone 123 was only 30% at best. Since the octalone itself required a twelve step synthesis (Scheme IV) to prepare, we could not



124



126



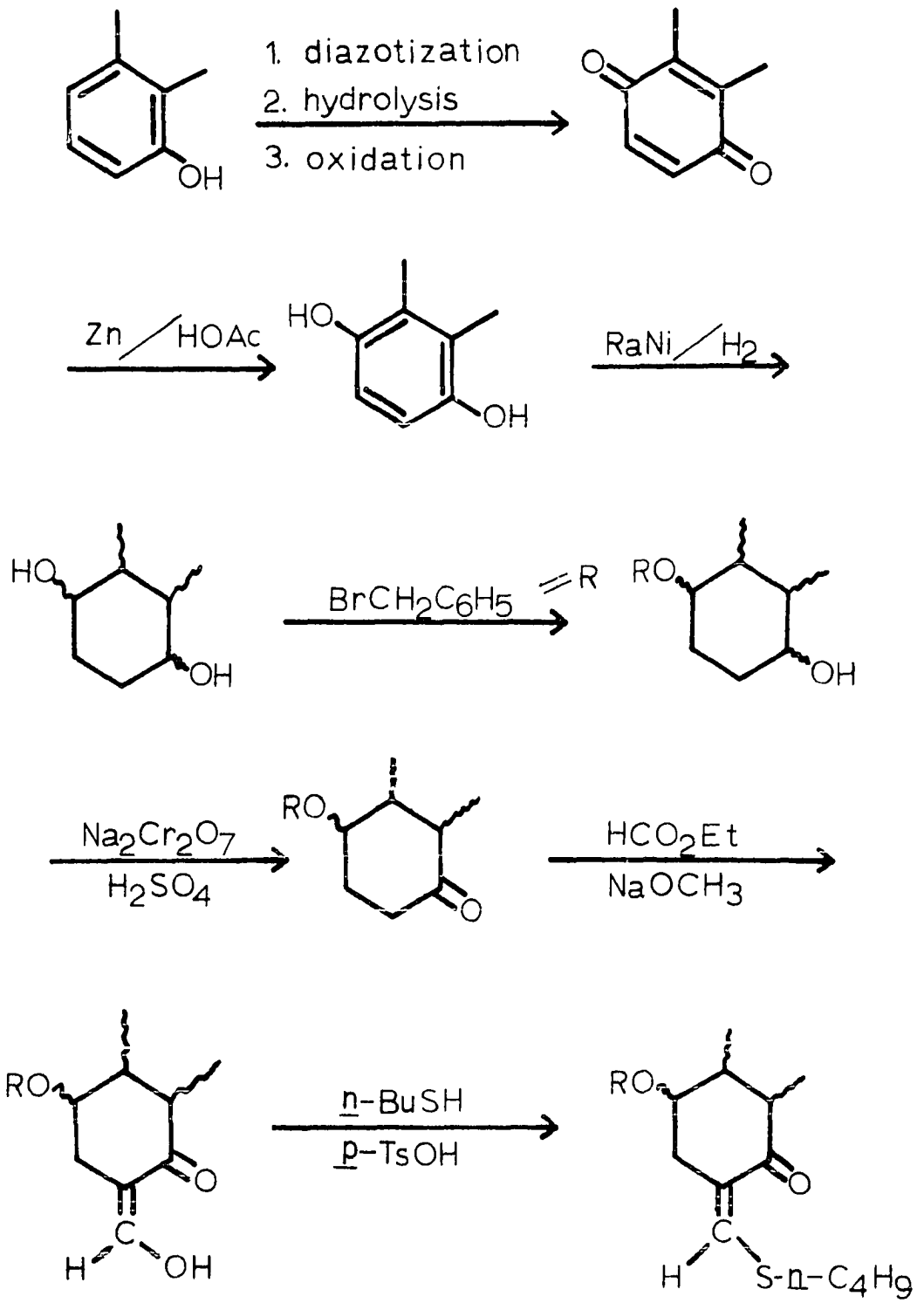
127

afford to suffer a 70% loss of material at this step and still hope to add the furan ring. Therefore this approach was set aside and a new approach to 98 was developed.

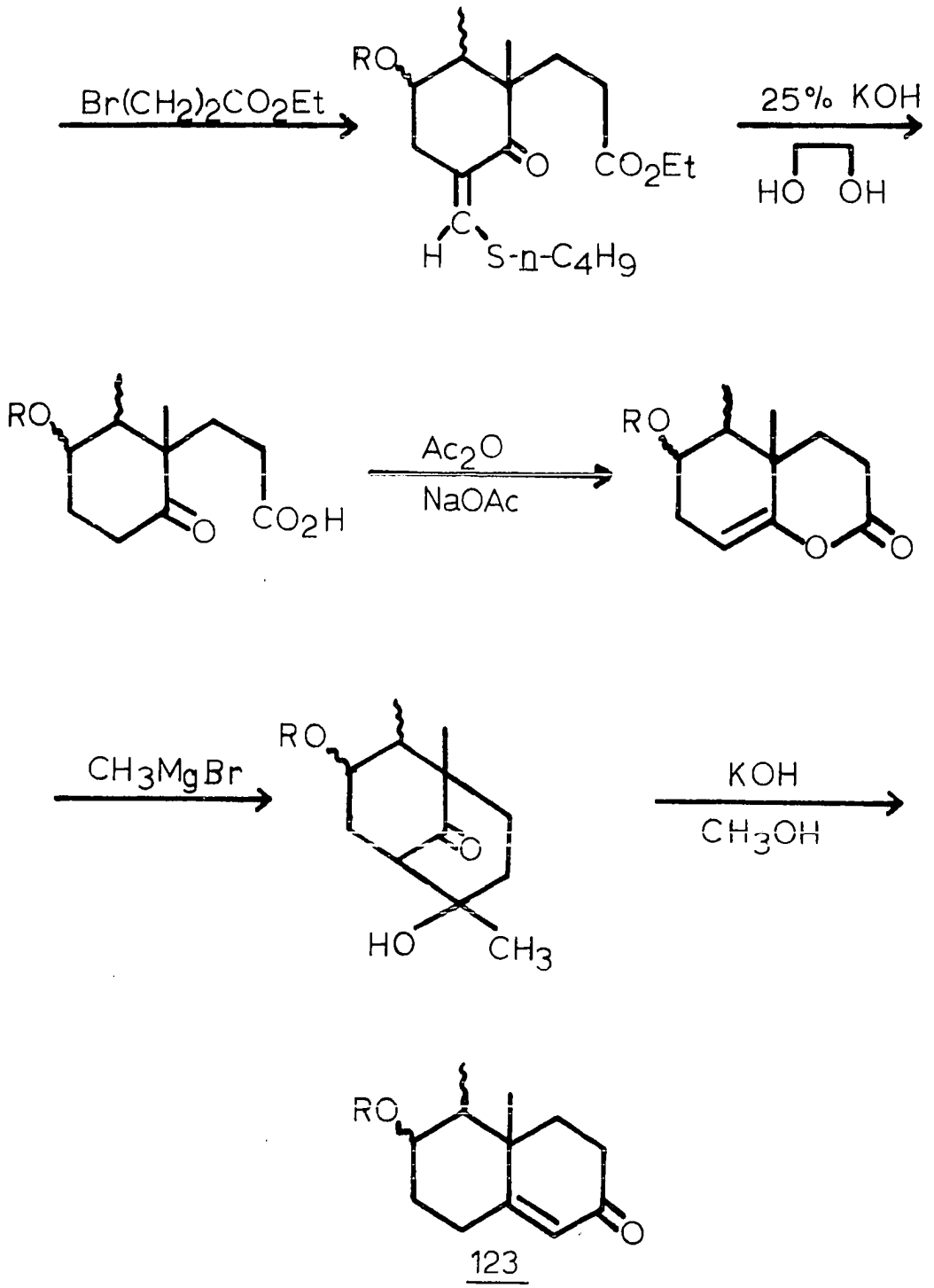
In an attempt to synthesize an intermediate enroute to petasin, Church et al., were able to prepare appreciable quantities of ketal-ketone 128 (114). While this compound itself was of no value to us, it was readily apparent that with a few modifications we could use a similar approach to yield benzyloxy ketone 98.

The necessary starting material for this route was 4,4a,5,6,7,8-hexahydro-5-hydroxy-4-methyl-2(3H)-naphthalenone (129). This compound is now readily available due to the elegant selective reduction developed by Boyce and Whitehurst (115). These workers found that reduction of

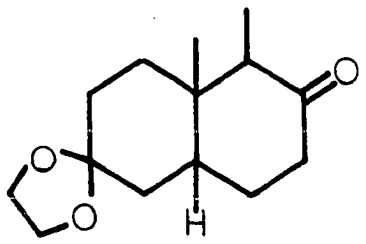
Scheme IV


1. diazotization
2. hydrolysis
3. oxidation
Zn / HOAc
RaNi / H2
BrCH2C6H5
R
Na2Cr2O7
H2SO4
HCO2Et
NaOCH3
n-BuSH
p-TsOH
S-n-C4H9

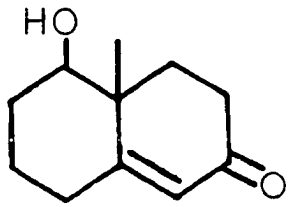
Scheme IV (Cont.)




123



128

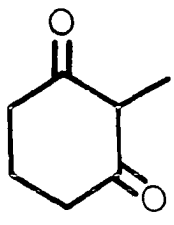


129

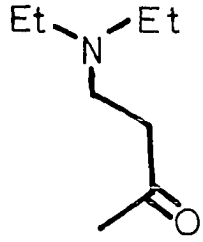
octalin-1,6-dione 130 with exactly one equivalent of freshly recrystallized sodium borohydride in ethanol for thirty minutes gives the desired hydroxy ketone in yields as high as 91%. In our hands, this reduction proceeded in yields ranging from 85-95%.

The necessary dione was itself prepared by condensation of 2-methyl-1,3-cyclohexanedione (131) with the Mannich base (132) (116). Both the Mannich base (1-N,N-diethylamino-3-butanone) and 2-methyl-1,3-cyclohexanedione were amenable to large scale preparation. The Mannich base was best prepared in low yield but high quantity by the method of Hagenmeyer (117). The better known procedure of Wilds et al., (118) proved to be erratic as has been noted by others (116).

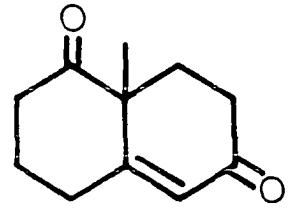
Two methods have been reported for the preparation of 2-methyl-1,3-cyclohexanedione. Although both methods were tried, useful quantities of this compound in pure form could best be obtained by the method of Thomson (119). This procedure involves the reduction of resorcinol using hydrogen and



131




132



130

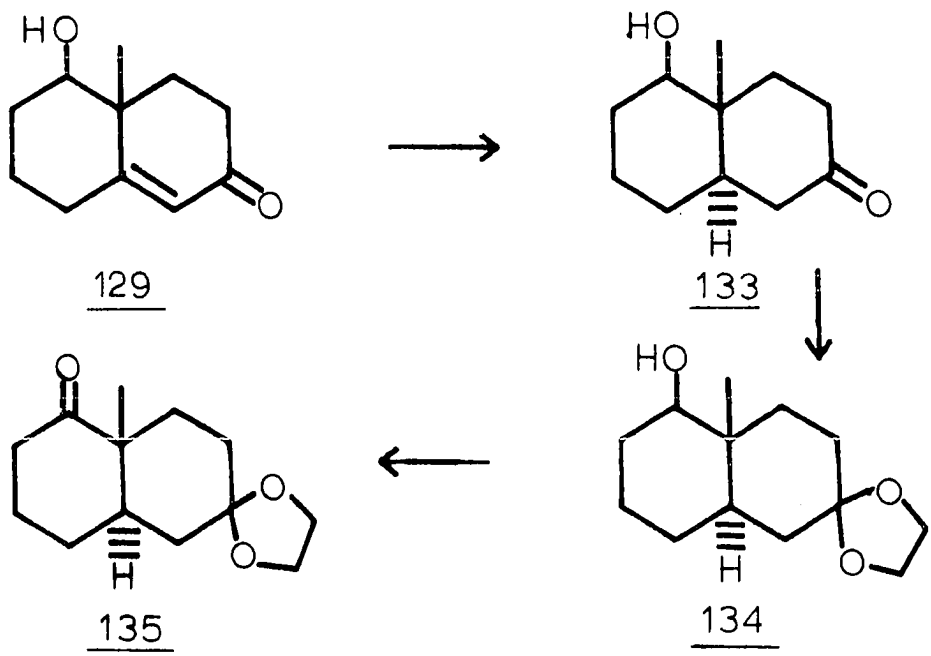
W-2 Raney nickel (120) at 2000 psi, followed by alkylation with methyl iodide. Although the yields were seldom over 50%, the material was sufficiently pure to be used directly in subsequent steps and could be prepared in large enough quantities (100-120 g) to make this method practical.

The other preparation of this compound (121), via cyclization of methyl-5-oxoheptanoate, requires the tedious synthesis of methyl-5-oxoheptanoate from glutaric anhydride (122), cyclization, and recrystallization. After a brief investigation, this method was discarded as being too time consuming.

Once we had sufficient hydroxy ketone (129) in hand, we began our synthesis of intermediate 98. Needing a trans ring fusion we again utilized the Birch reduction obtaining keto alcohol 133 in yields of 70% after purification by column chromatography.

The ketone was then protected by reaction with 1,2-ethanediol to form the hydroxy ketal 134. This hydroxy

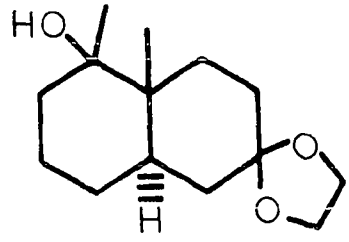
ketal (134) was then treated with Jones reagent (123) which oxidized it to the ketal ketone 135 in good yield.




129 133 135 134

Following the procedure used by Church, Ireland and Shridhar (114), this ketal ketone was treated with a ten-fold excess of methyl lithium (prepared from lithium containing 1% sodium) in refluxing ethyl ether overnight. Crude yields as high as 80% of hydroxy ketal 136 were obtained by this method. By means of this reaction, we now had completed the carbon skeleton required for intermediate 98. It remained only to introduce oxygen functionality at the 6-position, remove it from the 5-position, and cleave the ketal. The introduction of the hydroxy function was accomplished by the elegant method of Brown and his co-workers (124).

The crude hydroxy ketal was treated with iodine and heat, eliminating water to form olefin 137. Some cleavage of the ketal also occurred at this point and it was therefore necessary to re-treat the crude product with ethylene glycol and p-toluene sulfonic acid.

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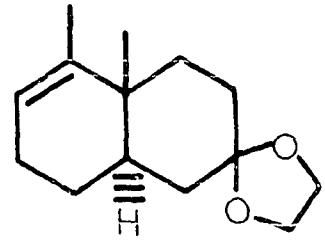
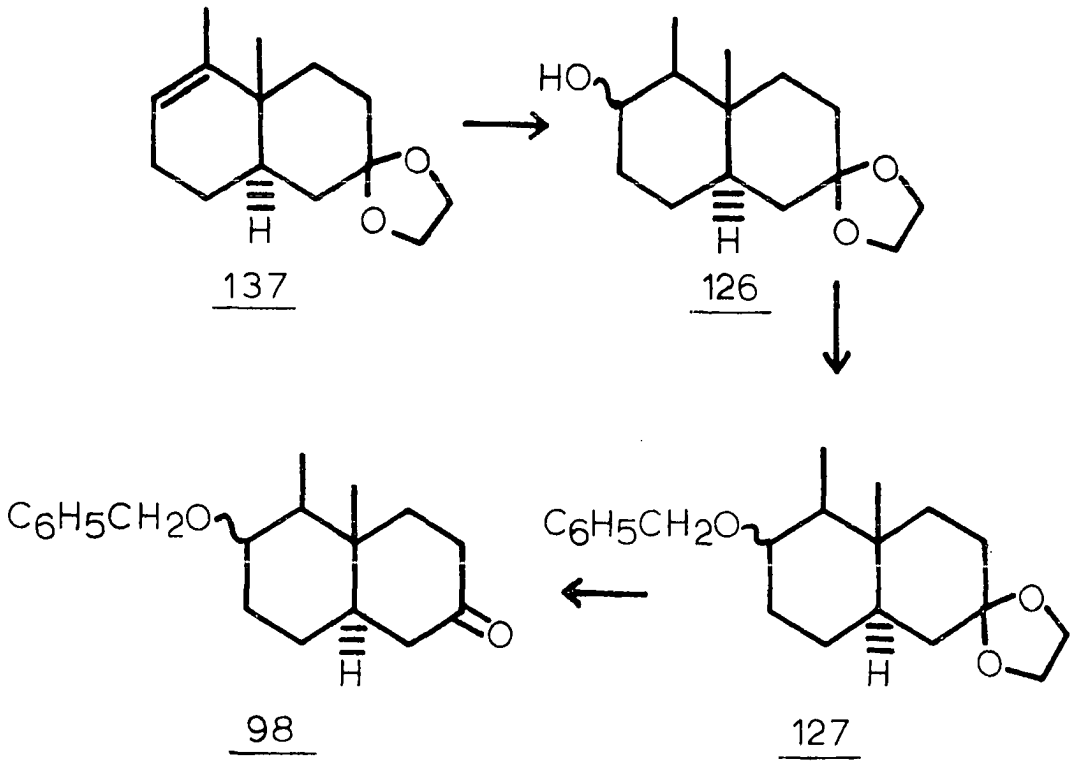



137

After purification by column chromatography, the desired 6-hydroxy function was introduced by treatment of the olefin with diborane generated *in situ* from sodium borohydride and boron trifluoride-etherate. This was followed by alkaline hydrogen peroxide treatment of the resulting organoborane complex to yield hydroxy ketal 126. The reaction proceeded in overall crude yield of 85%.

Treatment of compound 126 with excess benzyl bromide and base followed by hydrolysis of the ketal yielded the desired intermediate 98 in overall crude yield of 12% based on dione 130.

The benzyloxyketone (98) was purified by column chromatography and its spectra were identical with those of

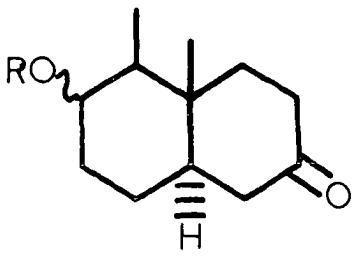



137 126 127 98

the benzyloxy ketone prepared by the method previously discussed. Analytical data (C,H analysis) also were in agreement with the structure proposed for 98. No attempt was made at determining the stereochemistry of the 5-methyl substituent or the 6-benzyloxy substituent. Since eventually the benzyl group would be removed and the resulting hydroxyl group oxidized to a ketone, the stereochemistry at these positions was at this point unimportant.

## Attempts to Convert Decalin 98 to Warburgin

We had now successfully completed the first two phases of the research problem. The important starting material (98) was now available and the method for converting it to the non-isoprenoid furanosesquiterpene, warburgin, had been developed on a model system. The task of combining these two phases of the synthesis was not anticipated to present any new or unsolvable problems. Unfortunately, as is often the case in any untried synthesis, problems did arise.

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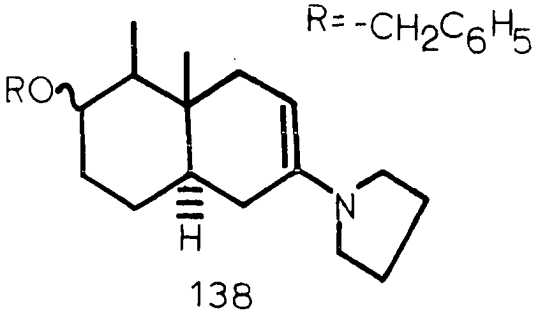


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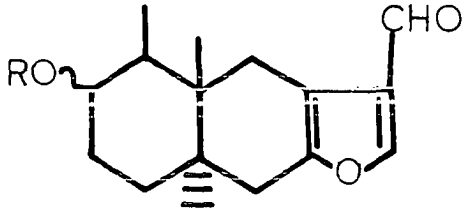


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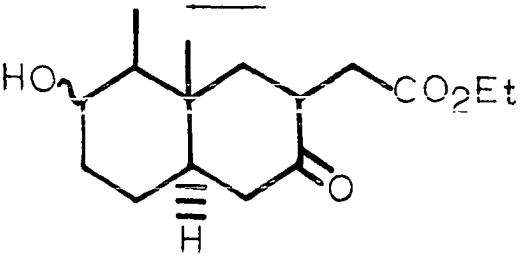
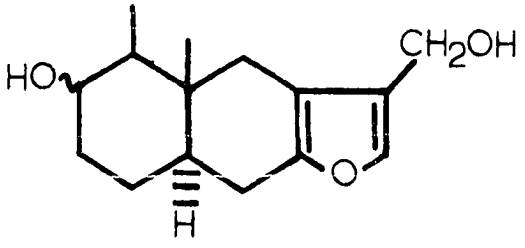



139

We proposed to alkylate the benzyloxy ketone 98 *via* its enamine (138) with ethyl bromoacetate as we had cyclohexanone *via* its enamine in the model studies. After the alkylation, we would proceed exactly as before with preparation of furan derivative 140.

From compound 140 to warburgin the necessary steps involved removal of the benzyloxy protecting group (which would entail simultaneous reduction of the aldehyde to the alcohol) yielding diol 141. This compound would then be oxidized to keto acid 142 and the acid esterified to form the methyl ester 143.

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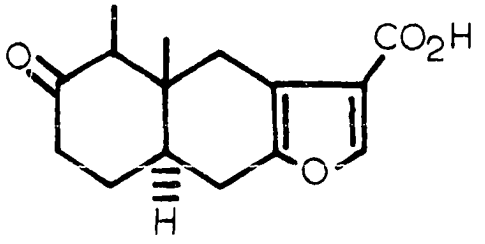


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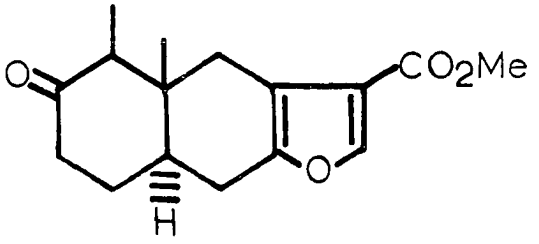
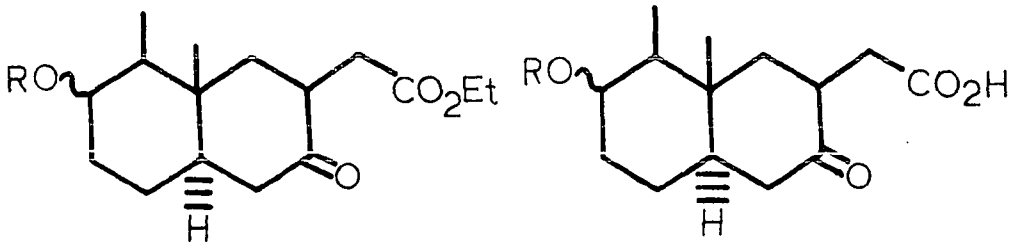



143

Compound 143 is the known (79) tetrahydrowarburgin which has been prepared from warburgin by catalytic hydrogenation. Since the physical and spectral properties of this compound have been reported and since tetrahydrowarburgin is stable while warburgin itself is not, this would be a suitable completion of the project.

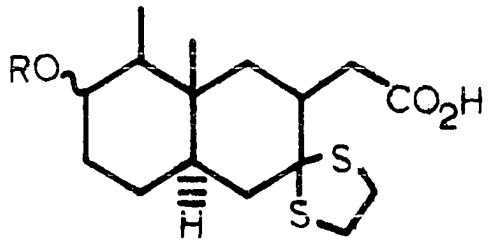
Complications, however, arose with the first step. It proved to be very difficult to alkylate 98 in the normal

manner. Althouqh alkylations with ethyl bromoacetate on enamines ordinarily proceed in yields of 45-80%, (93), alkylation of enamine 138 proceeded in benzene in only 10% (by nmr) yield. Various attempts to increase the yield by varying the time of reflux (from 2 hr to 5 hr, 12 hr and 24 hr) failed. Different solvents (toluene, xylene, dioxane, and methanol) were tried. The more polar solvents led to dialkylation and resinification, while less polar solvents and the solvent mixtures (benzene-methanol) led to low yields, the best of which was 15-20%. Changing from the pyrrolidine enamine to the morpholine or piperidine enamines lowered the yields to the point that only starting material was recovered. Due to the time and effort involved in the preparation of the intermediate (98) we decided to proceed with the small amounts of benzyloxyketo ester 139 we had and attempt to introduce the furan ring. Purification of 139 was accomplished by conversion to acid 142 and extraction with mild base.




139 R=-$CH_2C_6H_5$ 144

The acid was treated as in the model system with ethanedithiol and ethereal boron trifluoride but here again problems were encountered. Instead of the expected thioketal derivative 145, a mixture of hydroxy ketone 146 and hydroxy thioketal 147 with only traces of the desired compound was found.

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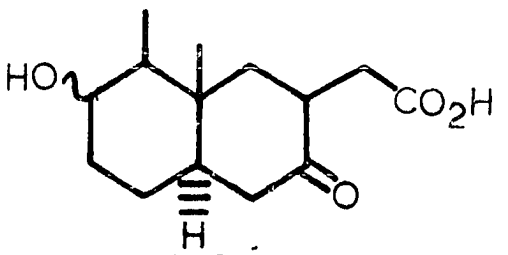


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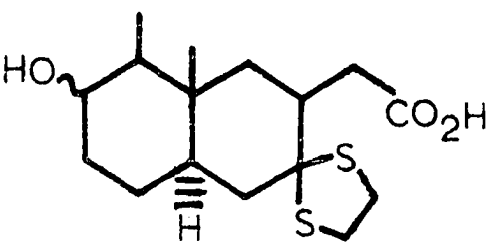


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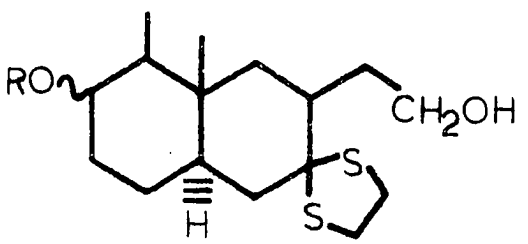


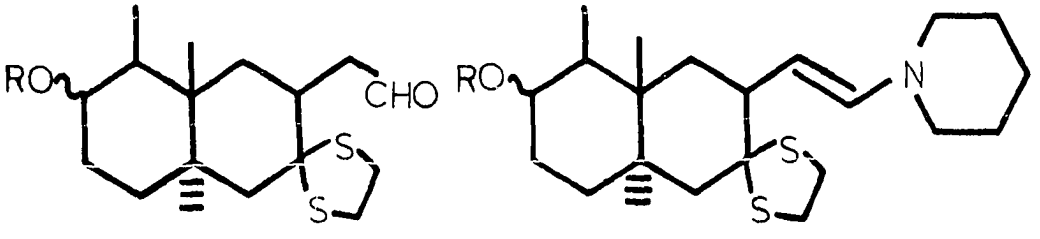

148

R=-$CH_2C_6H_5$

This problem was overcome by utilizing the method of Fieser (125) which uses acetic acid as the solvent. This procedure yielded the desired thioketal in 75% yield.

The thioketal was treated with lithium aluminum hydride in refluxing tetrahydrofuran reducing it to alcohol 148. This alcohol was then oxidized by the method used on the model system (DMSO-$SO_3$-pyridine) to give, in about 75% crude yield, aldehyde 149. This compound proved to be highly

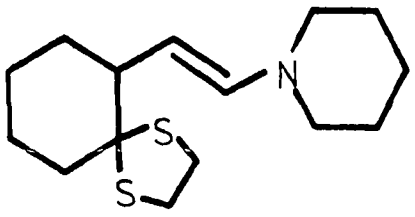
unstable, polymerizing in a period of 24 to 48 hours to an intractable black tar. Attempts at purification *via* the bisulfite addition product or chromatography resulted in rapid loss of material. The aldehyde (149) therefore was treated immediately with piperidine and potassium carbonate to form the enamine 150.




R=-$CH_2C_6H_5$

149 150

This compound, if kept under an inert atmosphere (nitrogen or argon) in a refrigerator, proved to be stable for a period of about three weeks. The high molecular weight and presence of the bulky substituents made purification of this compound very difficult. In addition, the sensitivity of enamines to oxygen and moisture is well known. We were therefore forced to use the crude enamine in the subsequent Vilsmeier reaction. We had however used crude enamine 120 in the model system for the same reaction and had not found any marked difference in the course of the reaction.

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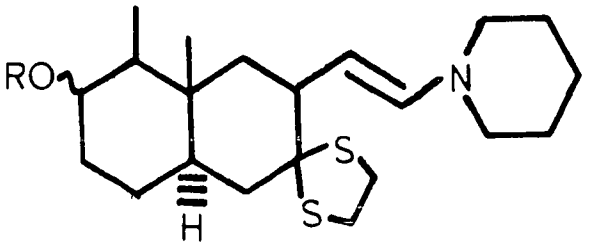


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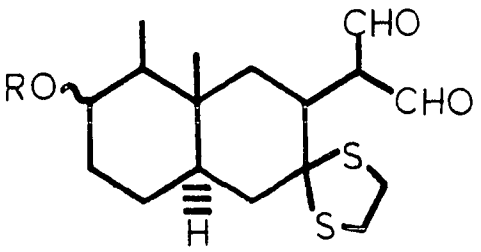


151

R=-$CH_2C_6H_5$

The success or failure of our synthesis now rested upon the answer to the question: will the Vilsmeier reaction on 150 yield the desired dialdehyde 151?

We tried the reaction under the range of conditions which we had used in the model system. Each attempt met with the same misfortune. The result was an unidentified red-brown oil which showed no aldehyde signal in the nmr and no carbonyl in the ir. Most attempts at purification of the oil led to formation of black intractable material.

At this point the cumulative effect of low yields in previous steps and the eventual failure of the Vilsmeier reaction forced abandonment of this approach to warburgin.

The use of the Vilsmeier reaction as the key step in the synthesis of 3-substituted furans proved in this case to be a stumbling block; however, the work on the model system demonstrated that in some cases this approach may be feasible. The growth of synthetic organic chemistry is closely tied to the development and investigation of new alkylating reactions and in this sense the work done here was certainly of value.

The problem of the synthesis of furans, substituted with a functionalized methylene at the 3-position, remains to be solved.

# EXPERIMENTAL

## Reagents

Common solvents and chemicals were obtained from commercial sources and were generally used without purification. When anhydrous solvents were required, reagent grade materials were treated according to the following:

Diethyl ether (anhydrous) - distilled from a mixture of sodium-benzophenone, which displayed a constant purple color.

Tetrahydrofuran - distilled from a mixture of sodium-benzophenone, which displayed a constant purple color.

p-Dioxane - distilled from calcium hydride.

N,N-Dimethylformamide - distilled from barium oxide immediately before use.

Methylene chloride - washed with 5% sodium carbonate, water, and distilled from anhydrous potassium carbonate.

Dimethylsulfoxide - distilled from calcium hydride.

Pyridine - allowed to stand over potassium hydroxide overnight, then refluxed and distilled from barium oxide.

Triethylamine - distilled from barium oxide.

1,2-Dichloroethane - dried over anhydrous magnesium sulfate, then distilled.

Carbon tetrachloride - distilled from phosphorous pentoxide.

Benzene - distilled from a mixture of sodium-benzophenone, which exhibited a constant purple color.

Acetonitrile - distilled from phosphorous pentoxide.

## Characterization of Compounds

All melting points were determined on a Kofler Micro Hot Stage melting-point apparatus and are uncorrected. Infrared spectra were taken on a Perkin-Elmer Model 21 Double Beam Spectrometer, a Beckman IR 12 spectrometer, or a Beckman IR 18A spectrometer. Nmr spectra were recorded at ambient temperature on a Varian A-60 spectrometer or a Hitachi Perkin-Elmer R20-B spectrometer and chemical shifts are reported as parts per million ($\delta$ scale) from tetramethylsilane as an internal standard. Mass spectra were determined using an Atlas CH-4 mass spectrometer with a direct solid inlet system. High resolution mass spectra were determined using an AEI-MS-209 mass spectrometer. In most cases, only the molecular ion is reported. Microanalyses were performed by Ilse Beetz Microanalytical Laboratories, Kronach, West Germany.

Whenever needed chromatographic procedures were employed for separation and purification of products. Microanalytical, air-dried, thin-layer chromatography plates were prepared by immersion coating of microscope slides in a chloroform slurry of Merck silica gel H obtained from Merck Distributors, Brinkmann Instruments, Incorporated, Westbury,

New York. Column chromatography was performed on Baker analyzed silica gel (60-200 mesh). Elution solvents were established by microanalytical thin-layer chromatography, and column elution was followed by thin-layer examination of consecutive effluent aliquots.

## Preparation of Compounds

### Ethyl 2-(2-oxo-1-cyclohexyl)acetate (103)

The procedure of Segre et al., (126) was modified slightly. A mixture of 29.00 g (0.29 mol) of cyclohexanone and 85 g (1.18 mol) of pyrrolidine in 250 ml of anhydrous benzene was refluxed 4 hr in a round-bottomed flask equipped with a Dean-Stark water separator. At the end of this time the Dean-Stark trap was replaced by a Soxhlet extractor equipped with a thimble full of molecular sieves type 4A and was refluxed an additional 2 hr.

The solvent and excess pyrrolidine were then removed under reduced pressure. The resulting enamine (102) was then dissolved in 170 ml of anhydrous benzene and this solution was brought to a slow reflux. To this solution was carefully added 37.50 g (0.22 mol) of ethyl bromoacetate dropwise as a 1:1 solution in anhydrous benzene. Reflux was maintained for 1 hr after which the excess bromoester and all solvents were removed under reduced pressure. To the resulting salt-like mass was added 200 ml of methanol and 20 ml of water. The

solution was refluxed for 2 hr, cooled, and concentrated under reduced pressure. The resulting solution was extracted with three 75-ml portions of ethyl ether. The ethereal extracts were combined and washed with two 50-ml portions of 2N hydrochloric acid, 50 ml of 10% sodium bicarbonate, water, brine, and dried ($MgSO_4$). The solvent was removed under reduced pressure and the residue distilled, affording 28.2 g (0.15 mol - 70%) of ethyl 2-(2-oxo-1-cyclohexyl)acetate (103) as a colorless liquid: bp 132-134.5° (13mm); ir (film) 2872 (C-H), 1744 (C=O, ester), 1717 (C=O, ketone), 1455, 1179, 1035 $cm^{-1}$; nmr ($CCl_4$) δ 4.05 (q, 2H, J = 7Hz, $-CH_2-CH_3$), 1.40-2.90 (m, 11H), 1.22 ppm (d, 3H, J = 7Hz, $CH_2-CH_3$); mass spectrum (70 eV) m/e 184 ($M^+$).

Ethyl 2-(2,2-ethylenedioxy-1-cyclohexyl)acetate (107)

A 1-l., three-necked, round-bottomed flask was fitted with a Dean-Stark water trap, a reflux condenser and a gas-inlet tube, flushed with nitrogen and charged with a solution of 100.0 g (0.54 mol) of ethyl 2-(2-oxo-1-cyclohexyl)acetate (103) dissolved in 400 ml of anhydrous benzene. To this solution was added 40 g (0.64 mol) of 1,2-ethanediol and 500 mg of p-toluenesulfonic acid. The resulting suspension was heated slowly to reflux and held at reflux for 13 hr, during which time 9.0 ml of water was removed from the system. The Dean-Stark trap was replaced by a Soxhlet extractor containing 4Å molecular sieves, and the reaction mixture was

refluxed for an additional 2.5 hr. Following this treatment, the benzene solution was cooled, diluted with 200 ml of ethyl ether, and washed with three 75-ml portions of a saturated sodium bicarbonate solution, brine, and dried ($MgSO_4$). Removal of the solvent at reduced pressure, followed by distillation, afforded 100 g (0.44 mol - 81%) of ethyl 2-(2,2-ethylenedioxy-1-cyclohexyl)acetate (107) as a viscous colorless liquid: bp 124-128° (0.50mm); ir (film) 2885 (C-H), 1720 (C=O), 1445, 1080, 1015 $cm^{-1}$; nmr ($CCl_4$) δ 3.88 (q, 2H, J = 7 Hz, $-C\underline{H}_2-CH_3$), 3.86 (s, 4H, $-O-C\underline{H}_2-C\underline{H}_2-O-$), 1.30-2.60 (m, 11H), 1.22 ppm (d, 3H, J = 7Hz, $-CH_2-C\underline{H}_3$); mass spectrum (16 eV) m/e, 228 ($M^+$).

2-(2,2-Ethylenedioxy-1-cyclohexyl)ethanol

A solution of 2.28 g (0.06 mol) of lithium aluminum hydride in 250 ml of anhydrous ethyl ether was stirred in a 1-l., three-necked, round-bottomed flask under a nitrogen atmosphere. To this was added 23 g (0.10 mol) of ethyl 2-(2,2-ethylenedioxy-1-cyclohexyl)acetate (107) slowly via a pressure-equalizing dropping funnel after which the reaction mixture was stirred for 0.5 hr. The reaction mixture was carefully treated with 2.3 ml of water followed by 2.3 ml of 15% sodium hydroxide and 6.9 ml of water and allowed to stir an additional 4 hr. The white granular precipitate was removed by filtration and the resulting ethereal solution was dried ($MgSO_4$). Removal of the solvent under reduced pressure

followed by distillation afforded 18.2 g (0.098 mol - 98%) of a colorless viscous liquid: bp 112-114° (0.75mm); ir (film) 3440 (O-H), 2920 (C-H), 1450, 1088 $cm^{-1}$; nmr ($CCl_4$) δ 3.86 (s, 4H, -O-C$\underline{H}_2$- C$\underline{H}_2$-O-), 3.50 (t, 2H, $\underline{J}$ = 7Hz, -C$\underline{H}_2$-OH), 3.48 (broad s, 1H, -$CH_2$-O$\underline{H}$), 1.20-1.90 ppm (m, 11H).

Anal. Calcd for $C_{10}H_{18}O_3$: C, 65.91; H, 7.74. Found: C, 65.89; H, 7.70.

2-(2,2-Ethylenedioxy-1-cyclohexyl)acetaldehyde

A three-necked, 2-l. flask equipped with a mechanical stirrer was charged with 10 g (0.054 mol) of the distilled 2-(2,2-ethylenedioxy-1-cyclohexyl)ethanol dissolved in 500 ml of anhydrous methylene chloride. To this stirred solution was added a slurry of 80 g of Collins' reagent (102) in 200 ml of methylene chloride, which had been prepared by the method of Dauben et al., (103). After 0.5 hr the reaction mixture was diluted with 500 ml of ethyl ether and poured into a 2 l. separatory funnel. The residue was rinsed with three 100-ml portions of ethyl ether and these were added to the separatory funnel. The resulting solution was washed with six 75-ml portions of saturated aqueous sodium bicarbonate. The aqueous solutions were combined and back extracted with 150 ml of ethyl ether. The ethereal extracts were combined, washed with 50 ml of 2N hydrochloric acid, 75 ml of saturated sodium bicarbonate, three 75-ml portions of water, brine, and dried ($MgSO_4$). Removal of the solvents

under reduced pressure and distillation afforded 6.5 g (0.035 mol - 66%) of 2-(2,2-ethylenedioxy-1-cyclohexyl)acetaldehyde as a colorless liquid: bp 114-118° (0.50mm); ir (film) 2900 (C-H), 1720 (C=O), 1448, 1092, 1055 $cm^{-1}$; nmr ($CCl_4$) δ 9.58 (t, 1H, J = 1Hz, -CHO), 3.86 (s, 4H, -O-$CH_2$-$CH_2$-O-), 1.00-2.40 ppm (m, 11H); mass spectrum (70 eV) m/e 184 ($M^+$).

Anal. Calcd for $C_{10}H_{16}O_3$: C, 65.19; H, 8.76. Found: C, 65.13; H, 8.79.

1,1-Diethoxy-2-(2,2-ethylenedioxy-1-cyclohexyl)ethane

A 250-ml, round-bottomed flask was equipped with a Dean-Stark water removal trap and a condenser, flushed with nitrogen, and charged with 2.27 g (0.0124 mol) of 2-(2,2-ethylenedioxy-1-cyclohexyl)acetaldehyde, 150 ml of anhydrous benzene, 4 ml of absolute ethanol and 200 mg of p-toluenesulfonic acid. The mixture was refluxed 12 hr during which time about 0.2 ml of water was removed. The Dean-Stark trap was replaced with a Soxhlet extractor equipped with a thimble full of type 4A molecular sieves and refluxed for 6 hr. At the end of this time the reaction mixture was cooled, washed with two 50-ml portions of 10% sodium bicarbonate, two 50-ml portions of water, brine, and dried ($MgSO_4$). The solvent was removed under reduced pressure affording 2.86 g (0.011 mol - 88%) of 1,1-diethoxy-2-(2,2-ethylenedioxy-1-cyclohexyl) ethane as a colorless liquid: bp 95-105° (0.70mm); ir (film) 2910 (C-H), 1439, 1090, 1051 $cm^{-1}$; nmr ($CCl_4$) δ 4.35 (t, 1H,

$J_1 = J_2$ = 6Hz, -C<u>H</u>-$(OCH_2CH_3)_2$), 3.88 (s, 4H, -O-C<u>H</u>$_2$-C<u>H</u>$_2$-O-), 3.30-3.80 (m, 4H, -O-C<u>H</u>$_2$-$CH_3$), 1.10-2.45 (m, 11H), 1.26 ppm (t, 6H, <u>J</u> = 6Hz, -O-$CH_2$-C<u>H</u>$_3$).

<u>Attempted preparation of 2-(2,2-ethylenedioxy-1-cyclohexyl)malondialdehyde</u>

A. A modification of the Vilsmeier-Haack reaction, developed by Arnold and Sorm (87) was used. Two variations were investigated.

1. A 50-ml, round-bottomed flask equipped with a magnetic stirrer, ice cooling bath, and pressure-equalizing dropping funnel was charged with 2 ml of freshly distilled anhydrous ethylene dichloride. After cooling to 0°; 1 g of freshly condensed phosgene was added dropwise over 10 min to form the Vilsmeier reagent. After the reagent, a pale yellow solid, had formed, 2.6 g (0.01 mol) of the diacetal was added all at once as a cold (0°) solution in 2 ml of anhydrous ethylene dichloride. The cooling bath was removed and the reaction mixture was allowed to warm to room temperature. The reaction mixture was then heated to 70° for 15 min, cooled and excess reagent was decomposed with 5 g of ice and 8 ml of saturated potassium carbonate (frothing). This mixture was heated to 95° and the ethylene dichloride was distilled. The resulting mixture was cooled, extracted with three 10-ml portions of 2:1 benzene–ethanol, and extracts were combined and dried ($K_2CO_3$). Distillation under reduced

pressure afforded 2.2 g of a red-brown oil: bp 110-115° (0.75mm). The nmr spectrum showed the loss of most of the ethylenedioxy protecting group and little change in the diethyl acetal, indicating an undesired reaction had taken place: nmr ($CCl_4$) $\delta$ 10.00 (s, less than 1/4H, aldehyde), 4.01 (q, 4H, -O-C<u>H</u>$_2$-CH$_3$), 3.85 (s, 1/2H, -O-C<u>H</u>$_2$-C<u>H</u>$_2$-O-), 2.80-1.30 (m, 9H), 1.21 ppm (t, 6H, -O-CH$_2$-C<u>H</u>$_3$).

2. Essentially the same reaction was run but freshly distilled phosphorous oxychloride was substituted (in identical molar quantities) for phosgene. The product of this reaction was spectroscopically identical with the above.

B. A 500-ml, two-necked, round-bottomed flask was fitted with a mechanical stirrer, pressure-equalizing dropping funnel, flushed with nitrogen, immersed in an ice-water bath and charged with 2.70 g (0.05 mol) of sodium methoxide in 500 ml of anhydrous benzene. To the stirred suspension was added dropwise a mixture of 1.84 g (0.01 mol) of 2-(2,2-ethylenedioxy-1-cyclohexyl)acetaldehyde and 3.70 g (0.05 mol) of freshly distilled ethyl formate dissolved in 50 ml of anhydrous benzene. When the addition was complete (0.5 hr) the reaction mixture was allowed to warm to room temperature and was stirred for 4 hr. At the end of this time the mixture was cooled to 0° and 100 ml distilled water was added. The organic phase was separated and extracted with three 30-ml portions of 5% sodium hydroxide. The aqueous

layers were combined, cooled with ice, and 150 ml of ethyl ether was added. The solution was kept at 0° while being acidified with 6N hydrochloric acid to pH 6. The acidic aqueous layer was then extracted with three 100-ml portions of ice-cold ethyl ether and the ethereal layers were combined, washed with water, brine, and dried ($MgSO_4$). The solvent was removed under reduced pressure. The nmr and ir spectra of the resulting yellow oil were identical with those of the starting aldehyde. Repeated attempts to prepare the dialdehyde by this method resulted only in partial loss of the ethylene acetal moiety.

Attempted preparation of 5-(2-oxo-1-cyclohexyl)cyclopentadiene (112)

Thallium cyclopentadienide was prepared by the method of Nesmeyanov and Sokalik (127). Thallous sulfate (25 g, 0.05 mol) was dissolved in 200 ml of water containing 10 g (0.18 mol) of potassium hydroxide. When the solution was homogeneous, 5 g (0.76 mol) of freshly distilled (from the dimer) cyclopentadiene dissolved in 5 ml of methanol was added and the mixture was shaken for several minutes. The resulting pale yellow precipitate was filtered, washed several times with ice-cold methanol, and dried in a desiccator over potassium hydroxide pellets. The yield of dry thallous cyclopentadienide was 20 g - 98%.

The method of Corey et al., was used to attempt to alkylate the thallous cyclopentadienide. To 13.5 g (0.05 mol) of thallous cyclopentadienide in 50 ml of anhydrous ether at -20° under nitrogen was added 8.85 g (0.05 mol) of 2-bromocyclohexanone dropwise with stirring. After stirring for 5 hr at -20° the solution was cooled to -40° and filtered. Concentration of the ether solution under reduced pressure and at low temperature (less than 0°) afforded 8.20 g of a light yellow liquid whose ir and nmr spectra were identical with the starting bromoketone. Repeated efforts at higher temperatures and longer reaction times led to identical results.

Ethyl 2-(2,2-ethanedithio-1-cyclohexyl)acetate (104)

Following the published procedure (128), a 100-ml, round-bottomed flask was charged with 18.4 g (0.1 mol) of ethyl 2-(2-oxo-1-cyclohexanone)acetate (103) and 18.8 g (0.2 mol) of 1,2-ethanedithiol. To the solution was added 21 ml of boron trifluoride-etherate, dropwise, with stirring. The solution warmed noticeably, and turned cloudy, then clear yellow. After complete addition, the reaction mixture was stirred for 25 min, poured over ice and extracted with three 25-ml portions of ethyl ether. The ethereal extracts were combined, washed with brine, ice-cold 10% aqueous sodium hydroxide (four 25-ml portions), three times with brine and dried, ($MgSO_4$). The solvent was removed under reduced

pressure and the resulting liquid distilled affording 20 g (0.076 mol - 76%) of ethyl 2-(2,2-ethanedithio-1-cyclohexyl) acetate (104) as a colorless oil: bp 126.0-126.5° (0.42mm); ir (film) 2940 (C-H), 1740 (C=O), 1452, 1288, 1180, 1105, 1040, 980 $cm^{-1}$; nmr ($CCl_4$) δ 4.08 (q, 2H, J = 7Hz, O-$CH_2$-$CH_3$), 3.18 (s, 4H, -S-$CH_2$-$CH_2$-S-), 1.30-2.40 (m, 11H), 1.19 ppm (t, 3H, J = 7Hz, $CH_2$-$CH_3$); high resolution mass spectrum $M^+$ obs: 260.0907; calcd: 260.0905.

2-(2,2-Ethylenedithio-1-cyclohexyl)acetic acid (113)

To a solution of 4.50 g (0.022 mol) of ethyl 2-(2,2-ethylenedithio-1-cyclohexyl)acetate (104) in 100 ml of methanol was added 10 ml of 20% aqueous potassium hydroxide. The mixture was refluxed for a period of 12 hr then cooled and diluted with 100 ml of water. The methanol was removed under reduced pressure and the resulting liquid was acidified to pH 4 with dilute sulfuric acid. The aqueous solution was continuously extracted with ethyl ether for 24 hr. Removal of the ether under reduced pressure afforded 3.4 g (0.021 mol) of crude 2-(2,2-ethylenedithio-1-cyclohexyl)acetic acid (113) as a thick yellow oil: ir (film) 3300-2800 ($CO_2H$), 2920 (C-H), 1700 (C=O), 1430, 1015 $cm^{-1}$; nmr ($CCl_4$) δ 11.76 (s, 1H, -$CO_2H$), 3.22 (s, 4H, -S-$CH_2$-$CH_2$-S-), 1.2-2.5 ppm (m, 11H).

2-(2,2-Ethylenedithio-1-cyclohexyl)acetyl chloride (114)

To 5 g (0.025 mol) of 2-(2,2-ethylenedithio-1-cyclohexyl)acetic acid (113) dissolved in 100 ml of anhydrous benzene, was added 0.72 g (0.03 mol) of sodium hydride and the resulting mixture was stirred for 0.5 hr. At the end of this time 2.60 g (0.015 mol) of oxalyl chloride, dissolved in 50 ml of anhydrous benzene, was added dropwise with stirring over a 15-min period. The resulting solution was heated to reflux and held there for 0.5 hr. The reaction mixture was cooled, filtered, and the solvents were removed under reduced pressure affording 4.81 g (0.025 mol) of crude 2-(2,2-ethylenedithio-1-cyclohexyl)acetyl chloride (114) as a pale yellow oil: ir (film) 2940 (C-H), 1800 (C=O), 1450, 1090, 1040 $cm^{-1}$; nmr ($CCl_4$) δ 3.19 (s, 4H, -S-C$\underline{H}_2$-C$\underline{H}_2$-S-), 1.2-2.5 ppm (m, 11H).

The compound rapidly gave a precipitate when treated with alcoholic silver nitrate and was used without purification in the attempted synthesis of the aldehyde.

Attempted preparation of 1,1-diethoxy-2-(-oxo-1-cyclohexyl)ethane (115)

To 15 g (0.1 mol) of cyclohexanone pyrrolidine enamine (prepared in the usual manner), under nitrogen, 10 g (0.05 mol) of 2-bromoacetaldehyde diethyl acetal was added dropwise with stirring. The reaction mixture was refluxed 2 hr, cooled and 150 ml of methanol and 15 ml of water were added.

The resulting mixture was refluxed for 2 hr, cooled and extracted with three 75-ml portions of ethyl ether. The ethereal extracts were combined, washed with water, brine, and dried ($MgSO_4$). Distillation resulted in the recovery of cyclohexanone and pyrrolidine. No product was formed and repeated attempts with varied reaction times led to the same results.

2-(2,2-Ethylenedithio-1-cyclohexyl)ethanol (116)

The procedure was the same as that used to prepare 2-(2,2-ethylenedioxy-1-cyclohexyl)ethanol with the exception that anhydrous tetrahydrofuran was used as the solvent and the reflux temperature was correspondingly higher. Distillation afforded 92% thioacetal (116) as a clear viscous oil: bp 140-145° (0.2mm) which crystallized after standing for a long period of time to give malable white crystals: mp 53.5-54.5°; ir (melt) 3400 (broad, OH), 2930 (C-H), 1445, 1280, 1050, 980 $cm^{-1}$; nmr ($CDCl_3$) δ 3.55 (t, 2H, J = 7Hz, $CH-CH_2-OH$), 3.18 (s, 4H, $-S-CH_2-CH_2-S-$), 2.15-1.25 ppm (m, 11H).

Anal. Calcd for $C_{10}H_{18}OS_2$: C, 55.00; H, 8.31; S, 29.36. Found: C, 55.15; H, 8.17; S, 29.32.

2-(2,2-Ethylenedithio-1-cyclohexyl)acetaldehyde (105)

A. Following the procedure of Brown and Rao (100) a 250-ml, round-bottomed flask equipped with an overhead stirrer and a pressure-equalizing dropping funnel was charged with 15.0 ml of diglyme and 0.84 g (0.022 mol) of lithium

aluminum hydride. To the stirred suspension was added 2.51 g (0.022 mol) of t-butanol dropwise over a 1-hr period. The resulting light gray solution was used in the following preparation.

A solution of 4.22 g (0.022 mol) of acid chloride in 50 ml of diglyme, contained in a 250-ml, three-necked, round-bottomed flask equipped with an overhead stirrer, pressure-equalizing addition funnel, thermometer and flushed with nitrogen, was cooled to -78° with a Dry Ice–isopropanol bath. To this solution was added dropwise the previously described solution of lithium tri-t-butoxyaluminohydride over a 1-hr period. The cooling bath was removed and the mixture allowed to warm up over 1 hr and then was poured over crushed ice. The resulting mixture was extracted with three 50-ml portions of ethyl ether, washed with three 25-ml portions of water, brine and dried ($MgSO_4$). Removal of the solvent under reduced pressure afforded 4.1 g of a yellow liquid. The infrared spectrum shows the presence of a carbonyl group at 1800 $cm^{-1}$ and 1715 $cm^{-1}$ the latter being less intense. Nuclear magnetic resonance spectroscopy shows a very small peak at $\delta$ 9.52. The ratio of aldehyde to alcohol was estimated by integration of the nmr spectrum to be 1:7. Repeated attempts failed to improve the yield.

B. The method of Dauben et al. (103) was used as described in the preparation of 2-(2,2-ethylenedioxy-1-cyclo-

hexyl)acetaldehyde. The aldehyde was routinely obtained as a viscous, light tan oil in yields of 55-58%: bp 118-122° (0.55mm); ir (film) 2930 (CH), 2859 (aldehyde, CH), 1724 (C=O), 1447, 1025 $cm^{-1}$; nmr($CCl_4$) δ 10.70 (t, 1H, J = 1Hz, -CHO), 3.18 (s, 4H, -S-$CH_2$ -$CH_2$-S-), 1.10-2.50 ppm (m, 11H,); high resolution mass spectrum $M^+$ obs: 216.0659; calcd: 216.0661. 2,4-DNP, recrystallized from methanol, mp 147.5-148.5°, deep orange crystals.

Anal. Calcd for $C_{16}H_{20}O_4N_4S_2$: C, 48.47; H, 5.08; N, 14.13; S, 16.17. Found: C, 48.61; H, 4.99; N, 14.09; S, 16.12.

C. The method of Parikh and Doering (104) was employed utilizing a pyridine-sulfur trioxide 1:1 complex prepared by the method of Sisler and Audrieth (129). Other preparations of pyridine-sulfur trioxide (130-132) proved to be more difficult and yielded an impure product. A solution of 62 g (0.79 mol) of pyridine, freshly distilled from sodium hydroxide pellets, in 350 ml of anhydrous chloroform was placed in a three-necked, round-bottomed flask equipped with a thermometer, a mechanical stirrer, and a pressure-equalizing dropping funnel. The flask and contents were cooled below 0° in an ice-salt bath while 38.5 g (0.30 mol) of chlorosulfonic acid was added dropwise. Addition was completed after 1 hr, after which time the reaction mixture was filtered yielding white crystals which were washed with four

30-ml portions of ice-cold chloroform and dried under reduced pressure in a desiccator over phosphorous pentoxide. The yield was 96 g (0.18 mol - 60%) of almost pure pyridine-sulfur trioxide complex which is stable at room temperature if kept dry.

In a 125-ml, erlenmeyer flask, 3.83 g (0.023 mol) of pyridine-sulfur trioxide was dissolved in 20 ml of freshly distilled dimethylsulfoxide. In a second 125-ml, erlenmeyer flask, 1.7 g (0.008 mol) of thioacetal alcohol 116 and 4.7 g of triethylamine was mixed with 20 ml dimethylsulfoxide. The contents of the two flasks were rapidly stirred together and after 15 min the resulting red solution was acidified to pH 4 with 9M sulfuric acid added dropwise with cooling. The reaction mixture was extracted with three 25-ml portions of ethyl ether. The ethereal solution was washed with 25 ml of saturated sodium bicarbonate, water, brine, and dried ($MgSO_4$).

The resulting ethereal solution of crude aldehyde was purified by formation of the bisulfite addition product followed by regeneration with acid affording pure aldehyde (133,134). To the ethereal solution of crude 2-(2,2-ethylenedithio-1-cyclo- hexyl)acetaldehyde (105) was added 10 ml of methanol and 50 ml of 10% aqueous sodium bisulfite. The mixture was shaken for 2 hr and the resulting crystals were removed by filtration. The crystals were washed with two 10-ml portions of ice-cold ethyl ether then

placed in a 500 ml erlenmeyer flask with 100 ml of toluene. To this mixture was added 20 ml of 50% aqueous sulfuric acid and nitrogen was bubbled through the mixture while it was heated on a steam bath. When $SO_2$ could no longer be detected (about 2 hr) the mixture was cooled and the toluene was separated. The aqueous layer was then extracted with three 50-ml portions of ethyl ether. The ethereal extracts were combined, washed with 50 ml of saturated sodium bicarbonate, water, brine, and dried (type 4A molecular sieves). Removal of the solvent under reduced pressure afforded 1.31 g (0.0164 mol - 78%) of aldehyde as a colorless viscous liquid of high purity. Spectral data was identical with material prepared in part B (vide supra).

1,1-Diethoxyheptane

A 500-ml, round-bottomed flask, fitted with a Soxhlet extractor containing a thimble of type 4A molecular sieves, and condenser, was flushed with nitrogen and charged with 27 g (0.24 mol) of freshly distilled heptanal, 46 g (1.00 mol) of absolute ethanol, 500 mg p-toluenesulfonic acid and 150 ml of anhydrous benzene. The mixture was allowed to reflux through the molecular sieves for 24 hr. The reaction mixture was then cooled and washed with 50 ml of saturated sodium bicarbonate, water, brine, and dried (molecular sieves). Removal of the solvent under reduced pressure and distillation afforded 40 g (0.21 mol - 88%) of heptanal diethyl acetal as

a colorless liquid: bp 64° (0.15mm); ir (film) 2925 (C-H), 1465 (C-C), 1200, 1130, 1060, 1015 $cm^{-1}$ (acetal); nmr ($CCl_4$) δ 4.34 (t, 1H, $CH_2$-C<u>H</u>-$(OEt)_2$), 3.40 (q, 4H, O-C<u>$H_2$</u>-$CH_3$), 1.55-1.20 (m, 13H), 1.01 ppm (t, 6H, $CH_2$-C<u>$H_3$</u>).

<u>2-Formylheptanal</u>

The method of Arnold and Sorm (86) was followed. A 250-ml, three-necked, round-bottomed flask was fitted with an overhead stirrer and gas-inlet tube, and immersed in an ice bath. The flask was charged with 100 ml of ethylene dichloride and 18.7 g (0.26 mol) of dimethylformamide which had been freshly distilled from barium oxide. To the stirred dimethylformamide 16.75 g (0.11 mol) of distilled phosphorous oxychloride was added dropwise. After complete addition, 15 g (0.080 mol) of heptanal diethylacetal was added all at once. The ice bath was removed and the solution was heated to 83°. The reaction mixture was cooled and 40 g of ice and 80 ml of saturated potassium carbonate were added. The reaction mixture was heated to 85° to remove the ethylene dichloride by distillation. The reaction mixture was then cooled and extracted with three 50-ml portions of 1:1 ethyl alcohol-benzene. The solvents were removed under reduced pressure and the resulting red oil was dissolved in 100 ml of benzene. To this solution was added 20 ml of an acetate buffer (9.5 g sodium acetate, 19.1 g acetic acid, and 19.1 g water) and the reaction mixture was refluxed for 24 hr. The

mixture was then cooled, washed with three 20-ml portions of water, two 15-ml portions of 10% hydrochloric acid, two 10-ml portions of sodium bicarbonate, brine, and dried ($MgSO_4$). The solvents were removed under reduced pressure and the residue was distilled yielding 3 g (0.02 mol) of 2-formylheptanal as a colorless liquid which eventually solidified to a pale yellow mass: bp 90-105° (0.5mm); mp 51-54° [lit. (86) mp 55°]; ir (melt) 2925 (C-H), 2862 (C-H, aldehyde), 1685 (C=O), 1588, 1465 $cm^{-1}$; nmr ($CCl_4$) δ 9.8 (broad, 1/2H, enol), 8.17 (s, 1/2H, C<u>H</u>O), 6.55 (s, 1/2H enol), 2.5-1.9 (m, 2H, $C\underline{H}_2$-CH-$(CHO)_2$), 1.70-0.7 ppm (m, 10H). Typical yields varied widely and apparently randomly between 30-50%.

<u>2-Formyl-3-methylbutanal (119)</u>

The method of Stork <u>et al</u>., (92) was used to prepare the piperidine enamine of isovaleraldehyde (<u>118</u>). A 100-ml, round-bottomed flask fitted with a pressure-equalizing dropping funnel and a calcium chloride drying tube was flushed with nitrogen and charged with 50 g (0.59 mol) of piperidine and 14 g (0.11 mol) of anhydrous potassium carbonate. This mixture was cooled to 0° and 20 g (0.23 mol) of isovaleraldehyde was added dropwise with shaking. After the addition was complete (15 min) the apparatus was equipped with a magnetic stirrer and the mixture was stirred for 24 hr at room temperature. The mixture was then filtered and the

filter cake was washed with anhydrous ether. The washings were combined with the filtrate and the solvent was removed under reduced pressure. Distillation afforded 34.15 g - 95% of enamine 118 as a colorless liquid: bp 88-89° (19mm) [lit. bp 83.5-88.0° (18mm)]; ir (film) 2930 (C-H), 1648 (C=C), 1388 (C-$(CH_3)_2$), 1125 $cm^{-1}$; nmr ($CDCl_3$) δ 5.6 (d, 1H, J = 14Hz, $\underline{H}C(NC_5H_{10})$=C-), 4.10 (dd, 1H, $J_1$ = 14Hz, $J_2$ = 7Hz, -$\underline{H}$C=CH-N), 2.62 (m, 4H, N-($C\underline{H}_2)_2$-), 2.08 (octet, 1H, J = 7Hz, ($CH_3$) -C$\underline{H}$-CH=C-), 1.48 (m, 6H), 0.93 ppm (d, 6H, J = 7Hz, ($C\underline{H}_3)_2$-CH-).

The enamine was treated under the Vilsmeier conditions previously described in the preparation of 2-formylheptanal. A 48 hr treatment with acetate buffer followed by the usual work-up afforded crude dialdehyde 119 in 70% yield as pale yellow crystals: mp 61-62.5° [lit. (86) mp 62-63°]; ir (melt) 2930 (C-H), 2862 (C-H, aldehyde), 1648 (C=O), 1380, 1170 $cm^{-1}$; nmr ($CCl_4$) δ 8.04 (s, 2H, -C$\underline{H}$O), 2.78 (octet, 1H, $(CH_3)_2$-C$\underline{H}$-C), 1.62 (m, 1H), 1.17 ppm (d, 6H, ($C\underline{H}_3)_2$-CH-); mass spectrum (70 eV) m/e 114 ($M^+$).

This reaction was also run utilizing the corresponding morpholine and pyrrolidine enamines. The dialdehyde was obtained in much lower yields (51% and 43% respectively) in these cases.

2-(2,2-Ethanedithio-1-cyclohexyl)malondialdehyde (121)

Both of the methods previously described were attempted using aldehyde 105 as the starting material.

A. The diethyl acetal 117 was prepared from aldehyde 105 utilizing absolute ethanol and p-toluenesulfonic acid as before in the preparation of 1,1-diethyloxyheptane. This acetal proved to be unstable to distillation and was purified by column chromatography using 15% ethyl acetate in hexane as the eluent.

The reaction proceeded in about 85% yield affording 1,1-diethoxy-2-(2,2-ethylenedithio-1-cyclohexyl)ethane (117) as colorless oil: ir (film) 2932 (C-H), 1462 (C-C), 1205, 1140, 1063 $cm^{-1}$; nmr ($CCl_4$) δ 4.48 (dt, 1H, $J_1 = J_2 = 5Hz$, $-C\underline{H}-(OCH_2CH_3)_2$), 3.28-3.62 (m, 4H, $OC\underline{H}_2-CH_3$), 3.18 (s, 4H, $-S-C\underline{H}_2-C\underline{H}_2-S-$), 1.20-2.30 (m, 11H), 1.15 ppm (t, 6H, $\underline{J} = 7Hz$, $O-CH_2-C\underline{H}_3$).

The Vilsmeier reaction was attempted on the diethyl acetal (117) but repeated attempts afforded only aldehyde 105 and no dialdehyde was obtained.

B. 1-Piperidino-2-(2,2-ethylenedithio-1-cyclohexyl) ethane 120 was prepared from aldehyde 105 in the same manner as was the enamine of isovaleraldehyde.

The reaction gave the enamine in 88% yield: ir (film) 2938 (C-H), 2800, 1652 (C=C-N), 1451, 1392, 1194, 1130 $cm^{-1}$; nmr ($CCl_4$) δ 5.78 (d, 1H, $\underline{J}$ = 14Hz, $-CH-CH=C\underline{H}-N-$), 4.30 (dd,

1H, $J_1$ = 14Hz, $J_2$ = 8Hz, -CH-C<u>H</u>-CH-N), 3.12 (s, 4H, -S-C<u>H</u>$_2$-C<u>H</u>$_2$-S-), 2.6-2.8 (m, 4H, -C<u>H</u>$_2$-N-C<u>H</u>$_2$-), 2.30-1.20 ppm (m, 15H). This material was not purified, but was used directly in the preparation of dialdehyde 121.

The conditions utilized in the preparation of dialdehyde 121 from enamine 120 were similar to those described previously but two modifications were made. The amount of Vilsmeier reagent and the reaction time were both increased. A 250-ml, round-bottomed flask was equipped with a magnetic stirrer, ice-water cooling bath, and pressure-equalizing dropping funnel. The flask was purged with nitrogen and charged with 18 g (0.26 mol) of freshly distilled dimethylformamide and 50 ml of anhydrous ethylenedichloride. When this solution had cooled to 10°, 30.6 g (0.2 mol) of freshly distilled phosphorous oxychloride was added dropwise with stirring to form the pale pink Vilsmeier reagent. The enamine, 7 g (0.025 mol) was then added all at once and the stirred mixture was heated to reflux for 2 hr, then worked up as before. Treatment of the resulting oil with 25 ml of acetate buffer yielded 5 g of a yellow oil. The oil was dissolved in ice-cold ethyl ether and extracted with ice-cold 15% aqueous sodium hydroxide. The aqueous basic solution was mixed with 100 ml of ethyl ether and acidified with 2N hydrochloric acid at 0°. The organic layer was dried over molecular sieves at 0° for 24 hr and the solvent was removed

under reduced pressure at room temperature, affording 2.8 g (0.012 mol - 47%) of 2-(2,2-ethylenedithio-1-cyclohexyl) malondialdehyde (121) as a pale yellow solid. The solid was sublimed affording fine white crystals: mp 69.5-71°; ir (melt) 2925 (C-H), 2860 (C-H, aldehyde), 1652 (C=O), 1583, 1262, 1245 $cm^{-1}$; nmr ($CCl_4$) δ 8.30 (s, 2H, -CHO), 3.00-3.22 (m, 4H, -S-$CH_2$-$CH_2$-S-), 2.80-1.20 ppm (m, 10H).

Anal. Calcd for $C_{11}H_{16}O_2S_2$: C, 54.07; H, 6.60; S, 26.24. Found: C, 54.20; H, 6.44; S, 26.05.

4,5,6,7-Tetrahydro-3-benzofurancarboxaldehyde (100)

The method of Corey and Erickson (108) was followed. Dialdehyde 121 (4.6 g, 0.019 mol) was dissolved in 100 ml of 80% aqueous acetonitrile. A second solution consisting of 12 g (0.044 mol) of mercuric chloride and 2.2 g (0.022 mol) of calcium carbonate dissolved in 150 ml of 80% aqueous acetonitrile was also prepared. The two solutions were shaken together for 14 hr. The resulting light brown precipitate was removed by filtration and the filter cake was washed thoroughly with 1:1 hexane-dichloromethane and the organic layers were combined. The resulting solution was washed with 60 ml of 0.5M ammonium acetate, twice with 100 ml of brine, and dried over type 4A molecular sieves. Removal of the solvent under reduced pressure followed by chromatography (elution with 50% ethyl acetate in hexane) afforded 1.5 g (0.01 mol - 55%) of benzofuran 100 as a light

yellow oil. In related experiments yields of 59, 65, 70 and 72% were obtained by thorough washings of the filter cake, as much material appeared to adhere to it. Repeated chromatography yielded an almost colorless compound which darkens in a few hours and gives a positive ferric chloride test: ir (film) 2870 (C-H), 2730 (C-H, aldehyde), 1687 (C=O), 1543( $\nu$ furan), 1440, 1140 $cm^{-1}$; nmr ($CCl_4$) $\delta$ 9.99 (s, 1H, -CHO), 7.84 (s, 1H, furan), 2.20-1.40 ppm (m, 8H); high resolution mass spectrum $M^+$ obs: 150.0680; calcd: 150.0681.

The 2,4-DNP was prepared and recrystallized from ethyl acetate yielding deep red crystals: mp 155-156.5°; high resolution mass spectrum $M^+$ obs: 330.0956; calcd: 330.0964.

Anal. Calcd for $C_{15}H_{13}O_5N_4$: C, 54.56; H, 4.24; N, 16.97; Found C, 54.54; H, 4.35; N, 16.93.

Attempted preparation of Ethyl 2-(2,2-ethanedithio-1-cyclohexyl)-2-(formyl)acetate (122)

The piperidine enamine of aldehyde (105) was prepared as before by the method of Stork and his co-workers (92). A 500-ml, three-necked flask fitted with a 125-ml pressure-equalizing dropping funnel, a magnetic stirrer, and a condenser, was flushed with nitrogen and charged with 7 g (0.025 mol) of enamine 120 dissolved in 200 ml of anhydrous benzene. The mixture was brought to reflux and 4.1 g (0.03 mol) of freshly distilled ethyl chloroformate dissolved in 50 ml of benzene was added dropwise with stirring. After the

addition was complete the reaction mixture was refluxed for 5 hr. The resulting red solution was cooled and the solvent was removed under reduced pressure. The resulting red oil was treated with 200 ml of methanol and 20 ml of water and was refluxed 1 hr, then concentrated under reduced pressure. The resulting solution was extracted with three 75-ml portions of ethyl ether. The ether extracts were combined and washed with two 30-ml portions of 2N hydrochloric acid, 50 ml of 10% sodium bicarbonate, water, brine, and dried ($MgSO_4$). Removal of solvent under reduced pressure yielded only aldehyde 105. Repeated attempts led to identical results.

2-Methyl-1,3-cyclohexanedione (131)

The procedure of Thomson (119) was modified slightly. To a freshly prepared solution of 96 g (2.40 mol) of sodium hydroxide dissolved in 335 ml of distilled water was added 220 g (2.00 mol) of resorcinol. The resulting light tan solution was placed in a 1000-ml, packless autoclave together with 35 to 40 g of W-2 Raney nickel catalyst (120). The reaction mixture was stirred under 1700-2100 psi of hydrogen at 45-50° for 72 hr. The uptake of hydrogen was not measured. The catalyst was removed by filtration with the aid of 100 ml of distilled water. To the resulting solution of 1,3-cyclohexanedione was immediately added 33.5 ml (0.40 mol) of concentrated hydrochloric acid, 145 ml dioxane, and 335 g (2.36 mol) of methyl iodide. This solution was refluxed for a

total of 12-14 hr; after 7 hr an additional 33.5 g (0.24 mol) of methyl iodide was added. At the end of the reflux the solution was cooled in an ice bath for 2 hr and the crystalline precipitate was collected by suction filtration and washed with four 200-ml portions of ice-cold water affording 120-150 g - 50% of 2-methyl-1,3-cyclohexanedione as light yellow crystals: mp 202-206°d [lit. (119) mp 208°d]; ir (nujol mull) 1565 (-OCCHCH CO; intermolecularly H bonded), 1450, 1360, 1080 $cm^{-1}$; nmr ($d_6$-DMSO) δ 9-11.00 (broad s, 1/2H, enol), 2.60-1.70 (m, 7 1/2H), 1.62 ppm (d, 3H, $-CH_3$); mass spectrum (70 eV) m/e 126 ($M^+$).

4-N,N-Diethylamino-2-butanone (132)

The procedure of Hagenmeyer (117) was followed. Acetone, 700 g 12 mol, diethylamine hydrochloride (6 mol as a 30% aqueous solution-prepared by the addition of 439 g diethylamine, 1157 ml of water and 500 ml of concentrated hydrochloric acid), paraformaldehyde (240 g 8.0 mol), and 150 ml of isopropanol were mixed and refluxed for 8-10 hr. At the end of this time the excess acetone was removed under reduced pressure and 500 g of 50% aqueous sodium hydroxide was added slowly with cooling. The amine layer was separated, dried ($Na_2SO_4$), and distilled affording 450 g (3.2 mol) of 4-N,N-diethylamino-2-butanone (132) as a colorless liquid: bp 75-78° (26mm); ir (film) 2970 ($CH_3$), 2840 ($-CH_2-$), 1720 (C=O), 1470, 1390, 1220, 1080 $cm^{-1}$; nmr ($CCl_4$) δ 2.87-2.15

(m, 8H), 2.08 (s, 3H, $-COCH_3$), 1.00 ppm (t, 6H, $-CH_2-CH_3$).

3,4,8,8a-Tetrahydro-8a-methyl-1,6(2H, 7H) naphthalenedione (130)

The procedure of Swaminathan and Newman (118) was followed. A mixture of 151.2 g (1.20 mol) of 2-methyl-1,3-cyclohexanedione, 204 g (1.20 mol) of 4-N,N-diethyl-2-butanone, 104 g (1.32 mol) of pyridine, and 1.5 l. of benzene was refluxed under nitrogen in a 3-l. round-bottomed flask for 18 hr. At the end of this time the deep red solution was cooled and washed successively with 1.5 l. of 7.5% aqueous hydrochloric acid; 1.5 l. of water and 1 l. of brine. The resulting solution was dried ($MgSO_4$) and the solvents were removed under reduced pressure. Distillation afforded 128 g (0.72 mol - 60%) of a light yellow oil which crystallized on standing: bp 108-120° (0.05mm) [lit. bp 109-115° (0.05mm)]; mp 46-48° [lit. mp 46-48°]; ir (melt) 2910 (C-H), 1705 (C=O), 1665 (C=C-CO-), 1610 (-C=C-), 1450, 1225, 1140 $cm^{-1}$; nmr ($CCl_4$) δ 5.60 (s, 1H, vinyl), 3.00-1.50 (m, 10H), 1.43 ppm (s, 3H, angular $-CH_3$); mass spectrum (70 eV) m/e 180 ($M^+$).

4,4a,5,6,7,8-Hexahydro-5-hydroxy-4a-methyl-2(3H)-naphthalenone (129)

Following the procedure of Boyce and Whitehurst (115) a 500-ml, three-necked, round-bottomed flask was equipped with a magnetic stirrer, thermometer, and a pressure-equalizing

dropping funnel. The apparatus was cooled to 0°, flushed with nitrogen and charged with 27 g (0.15 mol) of diketone 130 dissolved in 200 ml of absolute ethanol. Sodium borohydride (Baker grade - 98%) 1.7 g (0.045 mol) dissolved in 200 ml of absolute ethanol at 0° was added dropwise with stirring over a 1-hr period. Upon complete addition, the reaction mixture was stirred an additional 15 min after which 3 ml of glacial acetic acid was added. The solvent was removed under reduced pressure and the residue was dissolved in 30 ml of chloroform and washed with 100 ml of distilled water. The organic layer was dried over molecular sieves and the solvents were removed under reduced pressure affording a yellow liquid. This, upon distillation, gave 25 g (0.14 mol - 93%) of 4,4a,5,6,7,8,8a-hexahydro-5-hydroxy-4a-methyl-2(3H) naphthalenone as a colorless liquid: bp 140-148° (0.2mm) [lit. bp 135-137° (0.2mm)]; ir (film) 3420 (OH), 2960 (C-H), 1632 and 1596 (conjugated C=O), 1450, 1435, 1050, 855 $cm^{-1}$; nmr ($CDCl_3$) δ 5.76 (sl. broad s, 1H, -C=C<u>H</u>-), 3.24-3.66 (m, 2H, -C<u>H</u>-O<u>H</u>), 2.60-1.32 (m, 10H), 1.21 ppm (s, 3H, angular -C<u>H</u>$_3$). The oil solidified when exposed to moist air: mp 58-59° [lit. mp 58-59°].

<u>trans-3,4,4a,5,6,7,8,8a-Octahydro-5-hydroxy-4a-methyl-2(1H)naphthalenone (133)</u>

The procedure of Birch <u>et al</u>. (112), was followed with slight modification leading to significantly higher yields.

Hydroxy ketone 130, 20 g (0.11 mol) was dissolved in 300 ml of anhydrous tetrahydrofuran. This solution was added to a stirred solution of lithium 1.16 g (0.60 mol) dissolved in redistilled (from sodium) liquid ammonia at -33°. After 105 min the reaction was rapidly quenched with sufficient ammonium chloride to discharge the deep blue color. Approximately 200 ml of ethyl ether was added and the ammonia was allowed to evaporate. Water (150 ml) was added and the resulting solution was extracted with three 100-ml portions of ethyl ether, the ethereal extracts were combined and washed with water, brine, and dried over type 4A molecular sieves. The solvents were removed and the resulting pale yellow oil was chromatographed on 100 g of 60-133 mesh Florisil[1] eluted with 1.5 l. of benzene affording 15.2 g (0.084 mol - 76 %) of 133 as a colorless viscous liquid which crystallized slowly on standing: mp 68-70° [lit. (135) mp 68-70°]; ir (melt) 3445 (OH), 2935 (CH), 2862 (CH of $CH_3$), 1717 (C=O), 1450, 1150, 1025, 995 $cm^{-1}$; nmr ($CDCl_3$) δ 3.00-3.25 (m, 1H, -C<u>H</u>OH), 2.94 (s, 1H, -CHO<u>H</u>) 2.00-2.55 (m, 4H, -C<u>H</u>$_2$-COC<u>H</u>$_2$), 1.92-1.10 (m, 9H), 1.02 ppm (s, 3H, angular -C<u>H</u>$_3$).

trans-6,6-Ethylenedioxydecahydro-8a-methyl-1-naphthol (134)

A 1-l. round-bottomed flask was equipped with a Dean-Stark water trap and condenser. The flask was flushed with

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[1]J. T. Baker trademark for activated magnesium silicate.

nitrogen and charged with 60 g (0.33 mol) of hydroxy ketone 133, 40 g (0.65 mol) of 1,2-ethanediol, 750 ml of anhydrous benzene and 400 mg of p-toluenesulfonic acid. The mixture was refluxed for 5 hr during which time 6 ml of water was collected. The Dean-Stark trap was replaced with a Soxhlet extractor equipped with a thimble full of molecular sieves and the reaction mixture was refluxed an additional 13 hr. The mixture was cooled, washed with two 150-ml portions of saturated bicarbonate. The aqueous layer was extracted with three 100-ml portions of benzene and the organic extracts were combined and washed with 150 ml of brine and dried over molecular sieves. Removal of the solvent under reduced pressure afforded a thich yellow oil which was chromatographed on silica gel (eluted with 10% ethyl acetate in hexane) to give 75.0 g (0.282 mol - 94%) of keto alcohol 134 as a colorless viscous liquid: ir (film) 3440 (OH), 2920 (CH), 1450, 1100, 1080, 1030 $cm^{-1}$; nmr ($CDCl_3$) δ 3.88 (s, 4H, -O-C$\underline{H}_2$-C$\underline{H}_2$-O-), 3.25-3.00 (m, 1H, -C$\underline{H}$-OH), 2.30-1.90 (m, 14H), 0.83 ppm (s, 3H, angular -C$\underline{H}_3$).

trans-6,6-Ethylenedioxy-3,4,4a,5,6,7,8,8a-octahydro-8a-methyl-1(2H)-naphthalenone (135)

The procedure of Church et al. (114) was followed. A 500-ml, round-bottomed flask was fitted with a gas-inlet tube, a magnetic stirrer, and a pressure-equalizing funnel. The flask was flushed with prepurified nitrogen and charged

with a solution of 22.6 g (0.1 mol) of trans-6,6-ethylenedioxydecahydro-8a-methyl-1-naphthol (134) dissolved in 150 ml of reagent grade acetone. The reaction mixture was cooled to 2° and treated with 25 ml (0.1 mol-equiv) of Jones reagent (123) over a 10-min period. The temperature was kept below 10°. The mixture was stirred an additional 10 min at 10° and then was diluted with 200 ml of brine and extracted with five 100-ml portions of ether. The ethereal extracts were combined and washed with three 25-ml portions of saturated sodium bicarbonate, brine, and dried over molecular sieves. Removal of the solvent under reduced pressure followed by trituration with hexane at -50° induced crystallization. The waxy crystals which were obtained melt at 25-30°. The oil and semisolid were chromatographed on silica gel. Elution with chloroform yielded a semisolid which after four recrystallizations from hexane afforded small white crystals: mp 45-47° [lit. (114) mp 47-48°]. Total yield was 20.2 g (0.091 mol - 91%). VPC analysis showed that the unrecrystallized material was about 95-98% pure. Ireland's work (114) indicates that the contaminant is probably the cis isomer. Spectral data for the trans compound are: ir (melt) 2930 (CH), 1710 (C=O), 1450, 1360, 1120, 1080 cm$^{-1}$; nmr ($CCl_4$) δ 3.75 (s, 4H, -O-C$\underline{H}_2$-C$\underline{H}_2$-O-), 3.00-1.10 (m, 13H), 1.05 ppm (s, 3H, angular -C$\underline{H}_3$).

trans-6,6-Ethylenedioxy-3,4,4a,5,6,7,8,8a-octahydro-1,8a-dimethyl-1-naphthol (136)

The procedure of Church et al. (114) was followed with the exception that the methyllithium was generated in situ. A 2-l. round-bottomed flask was equipped with a mechanical stirrer, a gas-inlet tube and a condenser which was topped with a mercury bubbler. The flask was charged with 400 ml of anhydrous ether and 5.6 g of lithium ribbon (1% sodium) and flushed with argon. A steady stream of argon was introduced at a sufficient rate to prevent the entry of any other gas through the bubbler. Methyl bromide was then bubbled into the solution until the lithium began to react-about 5 min. The rate of introduction of methyl bromide was then reduced. After 90 min the solution had turned to a slightly cloudy pale blue and the lithium had completely reacted. The addition of methyl bromide was stopped and 18 g (0.08 mol) of acetal ketone 135 was added dropwise with stirring as a solution in 400 ml of anhydrous ether. After completion of the addition, the reaction mixture was refluxed for 12 hr. The mixture was poured over 300 ml of ice-cold 30% aqueous ammonium chloride and extracted with three 100-ml portions of ethyl ether. The ethereal extracts were combined, washed with brine and dried over molecular sieves. Removal of solvent under reduced pressure followed by column chromatography (eluted with 8 l. of benzene) afforded 17 g

(0.071 mol - 89%) of trans-6,6-ethylenedioxy-3,4,4a,5,6,7,8,8a-octahydro-1,8a-dimethyl-1-naphthol as a viscous oil: ir (film) 3480 (OH), 2940 (CH), 1450, 1360, 1120, 1080 $cm^{-1}$; nmr ($CDCl_3$) δ 3.94 (s, 4H, -O-$CH_2$-$CH_2$-O-), 2.00-0.75 ppm (m, 2H).

Anal. Calcd for $C_{14}H_{24}O_3$: C, 69.96; H, 10.07. Found: C, 70.00; H, 9.89.

trans-6,6-Ethylenedioxy-3,4,4a,5,6,7,8,8a-octahydro-1,8a-dimethylnaphthalene (137)

A 250-ml, round-bottomed flask was fitted with a calcium chloride drying tube and a gas-inlet tube. The flask was flushed with nitrogen and charged with 70 g (0.29 mol) of alcohol 136 and heated to 145°. Over a 2-hr period, 3 g of iodine was added in small increments. The solution turned black and water was evolved and driven off with a steady stream of nitrogen. The reaction mixture was cooled and extracted with ether, washed with brine, and dried over molecular sieves. The crude product was shown by nmr to have lost about half of the ethylenedioxy protecting group and was therefore dissolved in benzene and refluxed in the presence of 1,2-ethanediol and p-toluenesulfonic acid as before. Chromatography (hexane–10%chloroform) of the resulting yellow-brown liquid yielded 40 g (0.18 mol - 62%): ir (film) 2940 (CH), 1455, 1380, 1090 $cm^{-1}$; nmr ($CCl_4$) δ 5.02-5.18 (m, 1H, -C=C-H-), 3.78 (s, 4H, -O-$CH_2$-$CH_2$-O-), 2.20-1.08 (m, 14H), 0.92 ppm (s, 3H, angular -$CH_3$); high res-

olution mass spectrum: M+ obs: 222.160; calcd: 222.162.

trans-6,6-Ethylenedioxydecahydro-1,8a-dimethyl-2-naphthol (126)

A. The method of Brown et al. (124) was followed. A 250-ml, round-bottomed flask was charged with 125 ml of anhydrous tetrahydrofuran, 0.86 g (0.023 mol) of 98% sodium borohydride, and 7.0 g (0.032 mol) of trans-6,6-ethylenedioxy-3,4,4a,5,6,7,8,8a-octahydro-1,8a-dimethylnaphthalene. The flask was then fitted with a magnetic stirrer, flushed with nitrogen, and sealed with a rubber septum. To the well stirred suspension, 4.22 g of redistilled boron trifluoride-etherate was added dropwise via a syringe. The reaction mixture was stirred at room temperature for 3 hr and then was treated with 25 ml of 10% aqueous sodium hydroxide (septum removed). The resulting mixture was heated on a steam bath and about 100 ml of tetrahydrofuran was removed by distillation. At this time 25 ml of 30% hydrogen peroxide was added dropwise while maintaining a gentle reflux. After an additional 0.5 hr, the mixture was poured into 200 ml of cold water and extracted with three 100-ml portions of ethyl ether. The ethereal extracts were combined, washed with water, brine, and dried over type 4A molecular sieves. The solvent was removed under reduced pressure and the resulting viscous yellow oil was chromatographed on silica gel affording 6.46 g (0.027 mol - 84%) of trans-6,6-ethylenedi-

oxydecahydro-1,8a-dimethyl-2-naphthol (126) as a pale yellow oil which could not be crystallized: ir (film) 3420 (OH), 2920 (CH), 1445, 1355, 1270, 1100, 1030, 960 $cm^{-1}$; nmr ($CDCl_3$) δ 3.97 (s, 4H, -O-C$\underline{H}_2$-C$\underline{H}_2$-O-), 3.55-3.20 (broad s, -CH-O$\underline{H}$), 2.22-1.00 (m, 13H), 0.95 (s, 3H, angular -C$\underline{H}_3$), 0.89 ppm (d, 3H, -CH-C$\underline{H}_3$).

Anal. Calcd for $C_{14}H_{24}O_3$: C, 69.96; H, 10.07. Found C, 69.89; H, 10.03.

trans-2-Benzyloxy-6,6-ethylenedioxydecahydro-1,8a-dimethylnaphthalenone (127).

A 2-l., three-necked, round-bottomed flask was fitted with a mechanical stirrer, pressure-equalizing dropping funnel, reflux condenser and gas-inlet tube and flushed with prepurified nitrogen. Sodium hydride, 10.1 g (as a 56.8% dispersion in mineral oil) was added to the apparatus and the mineral oil was removed by three successive washings with 25-ml portions of pentane. The clear sodium hydride was covered with 20 ml of anhydrous dioxane and a solution of 42 g (0.175 mol) of trans-6,6-ethylenedioxydecahydro-1,8a-dimethyl-2-naphthol (126) in 400 ml of dry dioxane was added over a 35-min period. The mixture was stirred and heated to reflux for 6 hr and then allowed to cool to room temperature. A solution of 45 g (0.26 mol) of benzyl bromide (Aldrich Chemical Co.) in 300 ml of dry dioxane was added dropwise over 35 minutes to the stirred solution. The reaction mix-

ture was then heated to reflux for 18 hr. After allowing the mixture to cool to room temperature, 2.1 g of acetic acid in 200 ml of ethyl ether was added to decompose any residual sodium hydride. The mixture was diluted with 250 ml of anhydrous acetone and the precipitated sodium bromide was removed by filtration. The solvent was removed under reduced pressure and the residue was taken up in ethyl ether and washed with five 100-ml portions of water, brine, and dried (molecular sieves). Removal of the solvent under reduced pressure afforded 75 g of a crude yellow oil. The oil was chromatographed (15% ethyl acetate in hexane) yielding 51.4 g (0.156 mol) of trans-2-benzyloxy-6,6-ethylenedioxydecahydro-1,8a-dimethylnaphthalene (127) as a pale yellow oil: ir (film) 2920 (CH), 1455, 1360, 1200, 1100, 965 $cm^{-1}$; nmr ($CCl_4$) δ 7.14 (s, 5H, aromatic), 4.36 (q, 2H, J = 11Hz, $PhC\underline{H}_2$-O-), 3.72 (s, 4H, -O-$C\underline{H}_2$-$C\underline{H}_2$-O-), 3.25-3.00 (m, 1H, $C\underline{H}$O-H-Ph), 2.20-1.00 (m, 12H), 0.97 (broadened s, 3H, -CH-C-$\underline{H}_3$), 0.87 ppm (s, 3H, angular -$C\underline{H}_3$).

trans-6-Benzyloxy-4a,5-dimethyl-3,4,4a,5,6,7,8,8a-octahydro-2(1H)naphthalenone (98)

A 2-l. round-bottomed, three-necked flask was equipped with a reflux condenser and flushed with prepurified nitrogen. The flask was charged with 37 g (0.112 mol) of benzyloxy acetal 127 dissolved in 1 l. acetone. The reaction mixture was brought to reflux and 200 ml of 10% aqueous

hydrochloric acid was added. Reflux was continued for 15 min. The reaction mixture was cooled and sufficient solid sodium chloride was added to saturate the aqueous layer. The mixture was washed with 200 ml of brine and the aqueous washings combined and back extracted with three 200-ml portions of ethyl ether. The ethereal extracts were dried ($MgSO_4$) and the solvent was removed under reduced pressure affording 35 g of a dark yellow oil. The oil was chromatographed and eluted with 25% ethyl acetate in hexane affording 30 g (0.105 mol - 94%) of benzyloxy ketone 98 as pale yellow crystals: mp 75.5-77.5°; ir (melt) 2940 (C-H), 1720 (C=O), 1460, 1370, 1100, 1080 $cm^{-1}$; nmr ($CCl_4$) δ 7.13 (s, 5H, aromatic), 4.34 (q, 2H, J = 11Hz, $PhC\underline{H}_2$-O), 3.90-3.20 (m, 1H, $PhCH_2$-O-C<u>H</u>-), 2.30-1.00 (m, 12H), 0.97 (broad s, 3H, -CH-C<u>H</u>$_3$), 0.80 ppm (s, 3H, angular -C<u>H</u>$_3$).

Anal. Calcd for $C_{19}H_{26}O_2$: C, 79.68; H, 9.15. Found: C, 79.74; H, 9.05.

Ethyl 2-(trans-7-benzyloxydecahydro-8,8a-dimethyl-3-oxo-2-naphthalenyl) acetate (139)

The method of Stork et al., (92) was used to prepare the pyrrolidine enamine of benzyloxy ketone 98. A 250-ml, round-bottomed flask was fitted with a Dean-Stark water trap and a condenser. The flask was flushed with nitrogen and charged with 5.00 g (0.017 mol) of benzyloxy ketone 98 dissolved in 150 ml of benzene to which 8.5 g (0.12 mol) of pyrrolidine

had been added. The reaction mixture was refluxed 19 hr during which time 0.45 ml of water was collected. The Dean-Stark trap was replaced with a Soxhlet extractor equipped with a thimble full of molecular sieves and reflux was continued for an additional 8 hr. Solvent and excess pyrrolidine were removed under reduced pressure and the infrared spectrum of the residue was examined for traces of starting material (carbonyl), none remained. The enamine was dissolved in 100 ml of benzene and treated with 3.7 g (0.022 mol) of ethyl bromoacetate (dissolved in 50 ml of benzene) over a 0.5-hr period. The mixture was refluxed 24 hr, cooled, and the solvents were removed under reduced pressure. The residue was dissolved in 50 ml of methanol to which 5 ml of water had been added. The reaction mixture was refluxed 4 hr, cooled, and extracted with three 50-ml portions of ethyl ether. The ethereal extracts were combined and washed with water, brine, and dried over molecular sieves. Removal of the solvent under reduced pressure followed by column chromatography (eluted with 25% ethyl acetate in benzene) yielded 1.04 g (0.003 mol - 17%) of benzyloxy keto ester 139 as a pale yellow oil: ir (film) 3010 (aromatic, CH), 2920 (CH), 1774 (C=O, ester), 1717 (C=O, ketone), 1445, 1165, 1028 $cm^{-1}$; nmr ($CCl_4$) $\delta$ 7.14 (s, 5H, aromatic), 4.34 (q, 2H, Ph-$C\underline{H}_2$-O-), 3.98 (q, 4H, -O-$C\underline{H}_2$-$CH_3$), 3.00-0.85 (m, 17H), 0.82 ppm (s, angular -$C\underline{H}_3$); high resolution mass spectrum $M^+$ obs:

372.2305; calcd: 372.2300.

2-(trans-7-Benzyloxydecahydro-8,8a-dimethyl-3-oxo-2-naphthalenyl)acetic acid (144)

This compound was made in an effort to separate and purify ester 139 without resorting to column chromatography. The ester 139 was prepared as above. To 9 g (0.024 mol) of the crude mixture was added 100 ml of 10% ethanolic potassium hydroxide solution. The reaction mixture was stirred 20 hr and the ethanol was removed under reduced pressure. The resulting semisolid was dissolved in 600 ml of distilled water and washed with three 75-ml portions of ethyl ether. The aqueous layer was then acidified with 10% aqueous hydrochloric acid. The solution was thoroughly extracted with benzene and the organic layers were combined, washed with brine, and dried ($MgSO_4$). Removal of the solvent under reduced pressure afforded 6 g of crude acidic material which was shown by chromatography to contain 2.1 g (0.006 mol - 25%) of acid 144 as a viscous, glass-like yellow liquid which resisted attempts to crystallize: ir (film) 3400-2500 (acid), 2910 (CH), 1760 (acid), 1717 (C=O, ketone), 1479, 1288, 1246, 916 $cm^{-1}$; nmr ($d_6$-DMSO) $\delta$ 9.15 (broad s, not present when $D_2O$ added, 1H, -COOH), 7.12 (s, 5H, aromatic), 4.46 (q, 2H, $PhCH_2$-O-), 2.50-0.83 (m, 15H), 0.79 ppm (s, 3H, angular $-CH_3$).

2-(trans-7-Benzyloxydecahydro-8,8a-dimethyl-3,3-ethanedithio-2-naphthalenyl)acetic acid (145)

The compound was prepared both from the ester 139 and from the acid 144.

A. A 50-ml, one-necked flask, equipped with a magnetic stirrer was flushed with nitrogen and charged with 15 g (0.04 mol) of ethyl 2-(trans-7-benzyldecahydro-8,8a-dimethyl-3-oxo-2-naphthalenyl)acetate (139) and 9.0 g (0.095 mol) of 1,2-ethanediol. To the stirred mixture was added 8.4 ml of boron trifluoride-etherate, dropwise over a 10-min period. The reaction was stirred 25 min then poured over ice and extracted with three 40-ml portions of ethyl ether. The extracts were washed with brine, ice-cold 10% sodium hydroxide, brine, dried ($MgSO_4$) and the solvent was removed under reduced pressure. The crude residue was chromatographed on Florisil[1]. Elution with 10% ethyl ether in benzene afforded three fractions; the second of which contained 7.17 g (0.016 mol - 40%) of ethyl 2-(trans-7-benzyl-oxydecahydro-8,8a-dimethyl-3,3-ethanedithio-2-naphthalenyl)acetate which was dissolved in 10% ethanolic potassium hydroxide and hydrolyzed as before to yield 5.88 g (0.014 mol - 38%) of 2-(trans-7-benzyloxydecahydro-8,8a-dimethyl-3,3-ethanedithio-2-naphthalenyl)acetic acid as a gummy yellow semisolid.

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[1]J. T. Baker trademark for activated magnesium silicate.

The ir and nmr are identical with the spectra of material prepared in "B" below.

B. The method of Fieser (130) was followed. In a 50-ml, round-bottomed flask fitted with a magnetic stirrer, was placed a solution of 3.72 g (0.01 mol) of 2-(trans-7-benzyloxydecahydro-8,8a-dimethyl-3-oxo-2-naphthalenyl)acetic acid dissolved in 15 ml of acetic acid and 1.90 g (0.02 mol) of 1,2-ethanedithiol. As the solution was stirred, 2 ml of distilled boron trifluoride-etherate was added dropwise over a 5-min period. The solution was stirred 1 hr and poured over 25 g of ice. This mixture was extracted with three 25-ml portions of ethyl ether. The ethereal extracts were washed once with brine, four times with 25 ml of 10% aqueous sodium hydroxide, three times with 25 ml of brine, and dried over molecular sieves. Removal of the solvent yielded 4.05 g (0.096 mol - 96%) of thioacetal 145 as a viscous yellow oil: ir (film) 3400-2500 (acid OH), 2910 (CH), 1730 (C=O, acid), 1480, 1290, 1250, 920 $cm^{-1}$; nmr ($CCl_4$) δ 7.68 (broad s, not present when $D_2O$ added, -CO H), 7.14 (s, 5H, aromatic), 4.48 (q, 2H, $PhCH_2$-O-CH), 3.20 (s, 4H, -S-$CH_2$-$CH_2$-S-), 2.50-0.83 (m, 17H), 0.78 ppm (s, 3H, angular -$CH_3$). The material was not further purified but was used in the preparation of alcohol 148.

2-(trans-7-Benzyloxydecahydro-8,8a-dimethyl-3,3-ethane-dithio-2-naphthalenyl)ethanol (148)

A 1-l. three-necked, round-bottomed flask fitted with a pressure-equalizing dropping funnel, overhead stirrer, and a condenser was flushed with nitrogen and charged with 1.5 g (0.039 mol) of lithium aluminum hydride dissolved in 250 ml of anhydrous tetrahydrofuran. To the stirred solution was added 4.05 g (0.0096 mol) of thioacetal acid 145, dropwise as a solution in 50 ml of anhydrous tetrahydrofuran. The reaction mixture was refluxed for 6 hr. The mixture was cooled and 1.5 ml of water, 1.5 ml of 15% aqueous sodium hydroxide, and 4.5 ml of water were added sequentially. The resulting mixture was filtered and the solvent was removed affording 3.58 g (0.088 mol) of crude alcohol 148. The alcohol was chromatographed on Florisil[1]. Elution with benzene afforded 3.16 g (0.0078 mol - 81%) of alcohol 148 as a viscous pale yellow oil which crystallized (from hexane) to give small white crystals: mp 89.5-92.5°; ir (melt) 3400 (OH), 2920 (CH), 1460, 1391, 1070, 1028 $cm^{-1}$; nmr ($CDCl_3$) δ 7.14 (s, 5H, aromatic), 4.38 (q, 2H, Ph-$CH_2$-O), 3.20 (s, 4H, -S-$CH_2$-$CH_2$-S-), 3.00-0.80 (m, 19H), 0.75 ppm (s, 3H, angular -$CH_3$).

Anal. Calcd for $C_{23}H_{34}O_2S_2$: C, 67.93; H, 7.87; S,

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[1]Preparation of these compounds is given in the experimental section.

15.77. Found: C, 68.07; H, 7.72; S, 15.89.

2-(trans-7-Benzyloxydecahydro-8,8a-dimethyl-3,3-ethanedithio-2-naphthalenyl)acetaldehyde (149)

In a 125-ml erlenmeyer flask 1 g (0.0126 mol) of pyridine-sulfur trioxide complex (126) was dissolved in 15 ml of freshly distilled dimethylsulfoxide. In a second 125-ml erlenmeyer flask 1.00 g (0.0025 mol) of 2-(trans-7-benzyloxydecahydro-8,8a-dimethyl-3,3-ethanedithio-2-naphthalenyl) ethanol (148), 5 g (0.0495 mol) triethylamine and 10 ml of dimethylsulfoxide were combined. The contents of the two flasks were stirred together and heated to 50° for 30 min. The resulting deep red solution was cooled and acidified to pH 4 with 50% aqueous sulfuric acid and extracted with three 25-ml portions of ethyl ether. The ethereal solution was washed with 25 ml of saturated sodium bicarbonate, water, brine, and dried (molecular sieves).

The resulting solution was treated with 50 ml of 10% aqueous sodium bisulfite as before and the resulting addition product was washed with ether. Regeneration of the aldehyde with dilute acid afforded 0.72 g (0.0017, mol - 71%) of 2-(trans-7-benzyloxydecahydro-8,8a-dimethyl-3,3-ethanedithio-2-naphthanenyl)acetaldehyde (149) as a pale yellow oil: ir (film) 2920 (CH), 2720 (CH, aldehyde), 1718 (C=O), 1455, 1068, 1030, 959 $cm^{-1}$; nmr ($CCl_4$) δ 10.02 (s, 1H, aldehyde), 7.14 (s, 5H, aromatic), 4.48 (q, 2H, $PhCH_2$-O-), 2.98 (s, 4H,

-S-C$\underline{H}_2$-C$\underline{H}_2$-S-), 2.30-0.90 (m, 17H), 0.76 ppm (s, 3H, angular -C$\underline{H}_3$).

The stereochemistry of this compound was not determined. More than one isomer may be present.

The 2,4-DNP was prepared and recrystallized from 10% ethyl acetate in hexane: mp 125-128°.

<u>Anal</u>. Calcd for $C_{29}H_{36}N_4S_2$: C, 59.57; H, 6.21; N, 9.58; S, 10.97. Found: C, 59.40; H, 6.37; N, 9.36; S, 11.05.

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