AN APPROACH TO THE TOTAL SYNTHESIS OF APHIDICOLIN

Thesis by

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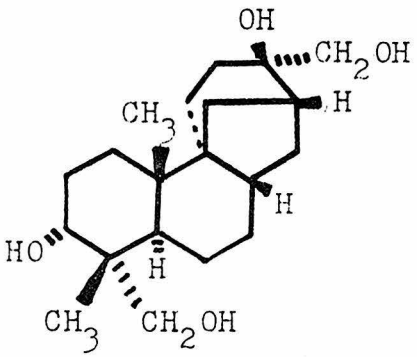
To Sharon, with love

Acknowledgements

I would like to thank Professor Robert E. Ireland for his guidance and encouragement. I would also like to extend my appreciation to my colleagues, for many stimulating discussions and fruitful suggestions. I offer a special thanks to my wife for her constant support and for helping to type this thesis. I thank the National Science Foundation and the California Institute of Technology for financial support.

Abstract

An approach to the total synthesis of the tetracyclic diterpene antibiotic aphidicolin i is described. The key intermediate ii was prepared in 19 steps (3% overall yield) from 2-methoxybenzosuberone. The key step involved the solvolysis of a spiro system (generated from a Claisen rearrangement) with participation of a remote double bond. The desired trans A/B ring fusion was introduced in the model system iii (18,19-dinoraphidicolan-3-one), available from alcohol ii in 7 steps (40% overall yield).



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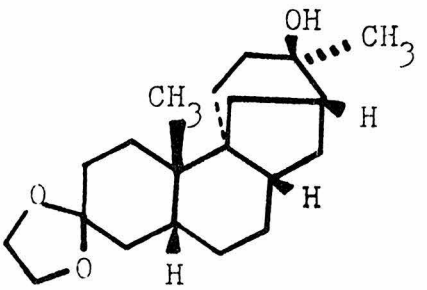

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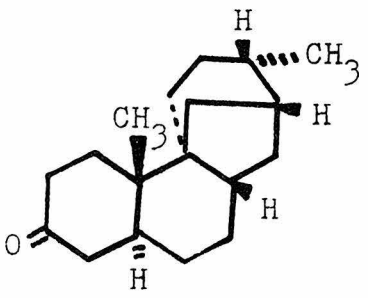

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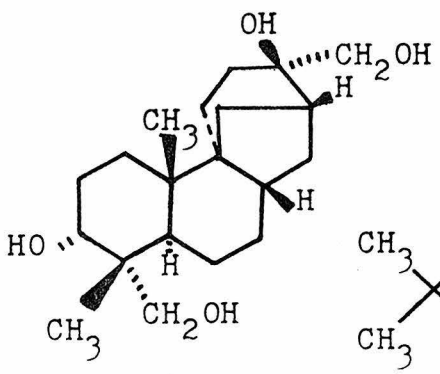
Introduction

Diterpenes are compounds which contain twenty carbon atoms and which are derived biogenetically from geranyl-geranyl pyrophosphate. They are primarily of plant and fungal origin and possess a wide variety of carbon skeletons. They have been the target of numerous successful syntheses. Dehydroabietic acid (1), pimaradiene and sandaracopimaradiene (2), rimuene (3), hibaene (4), and kaurene and atisirene (5) represent a few of the diterpenes which have succumbed to total synthesis in recent years. A listing of 619 diterpenes (complete through 1970) is available (6).

In 1972 Hesp reported the structure of aphidicolin (1), a tetracyclic diterpenoid tetraol antibiotic containing a novel bicyclo[3.2.1]octane ring system (7). The structure was determined through degradative and spectroscopic methods, and through the X-ray analysis of the bis-acetonide 2 (8). Hesp proposed that the parent



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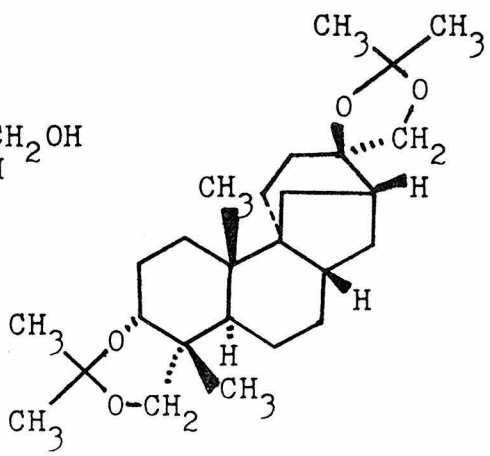

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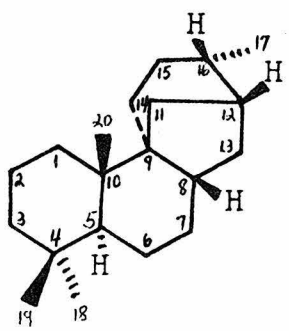

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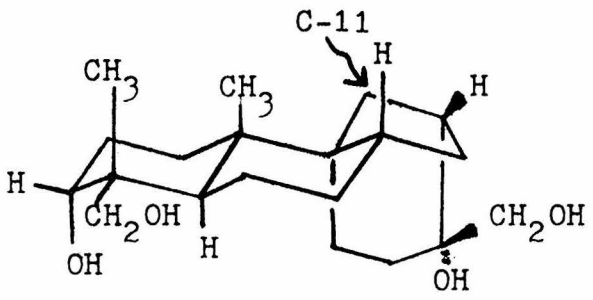
hydrocarbon be called aphidicolane (3) and be numbered as shown. Hence, aphidicolin is actually (+)-3∝,16,17,18-tetrahydroxyaphidicolane. The two stereo views (4 and 5) of aphidicolin should indicate that each of the six-membered rings is in the chair conformation, and the five-membered ring is in the envelope conformation with C-11 serving as the flap (7). The infrared spectra of aphidi-



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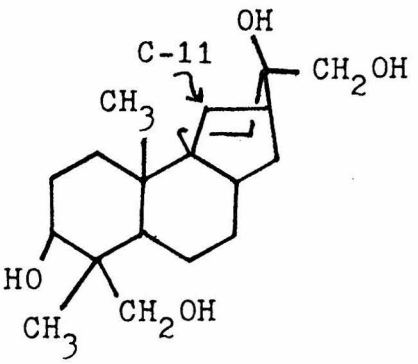

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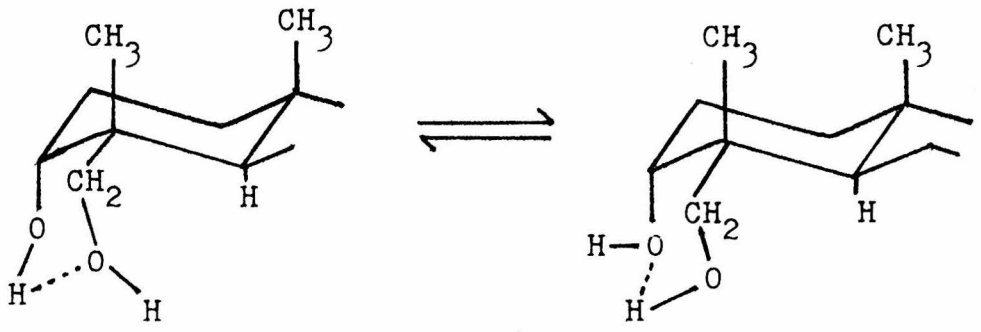
colin and various derivatives indicate extensive intramolecular hydrogen bonding between the secondary axial alcohol at C-3 and the primary alcohol at C-18.



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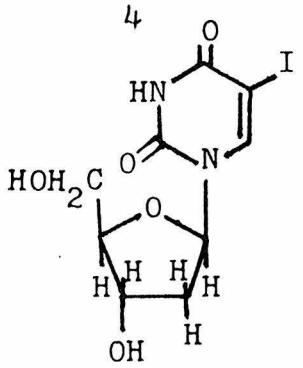
Aphidicolin ($C_{20}H_{34}O_4$, m.p. 227-233°C, $[\alpha]_D^{27}$ +12° [c 1.0, methanol]) was isolated by Hesp from cultures of Cephalosporium aphidicola Petch (7). Two years later Starratt and Loschiavo, while studying the interaction between the confused flour beetle (Tribolium confusum) and Nigrospora sphaerica (Sacc.) Mason (a fungus which grows on Canadian wheat, oat, and barley seeds), discovered that aphidicolin was also produced by the fungus (9). The aphidicolin that they isolated from Nigrospora sphaerica was in all respects identical to the mold metabolite from the Cephalosporium aphidicola fungus.

Aphidicolin has been shown to possess antiviral activity against a number of DNA-containing viruses, such as Herpes simplex, by inhibiting viral DNA synthesis (10). Herpes simplex is a variant of the virus responsible for cold sores and thought to be connected with cancer (11). For example, aphidicolin inhibits the growth of Herpes simplex type 1 in human embryonic lung cells with an activity of 0.2 ppm (10). Another potent inhibitor of cellular DNA synthesis is 5-iodo-2′-deoxyuridine (8). Idoxuridine is the most widely used drug in the treatment of human herpetic infections but suffers from the fact that Herpes simplex rapidly becomes resistant to it and that it is not without toxicity when given systemically to humans (10). On a molar basis, aphidicolin



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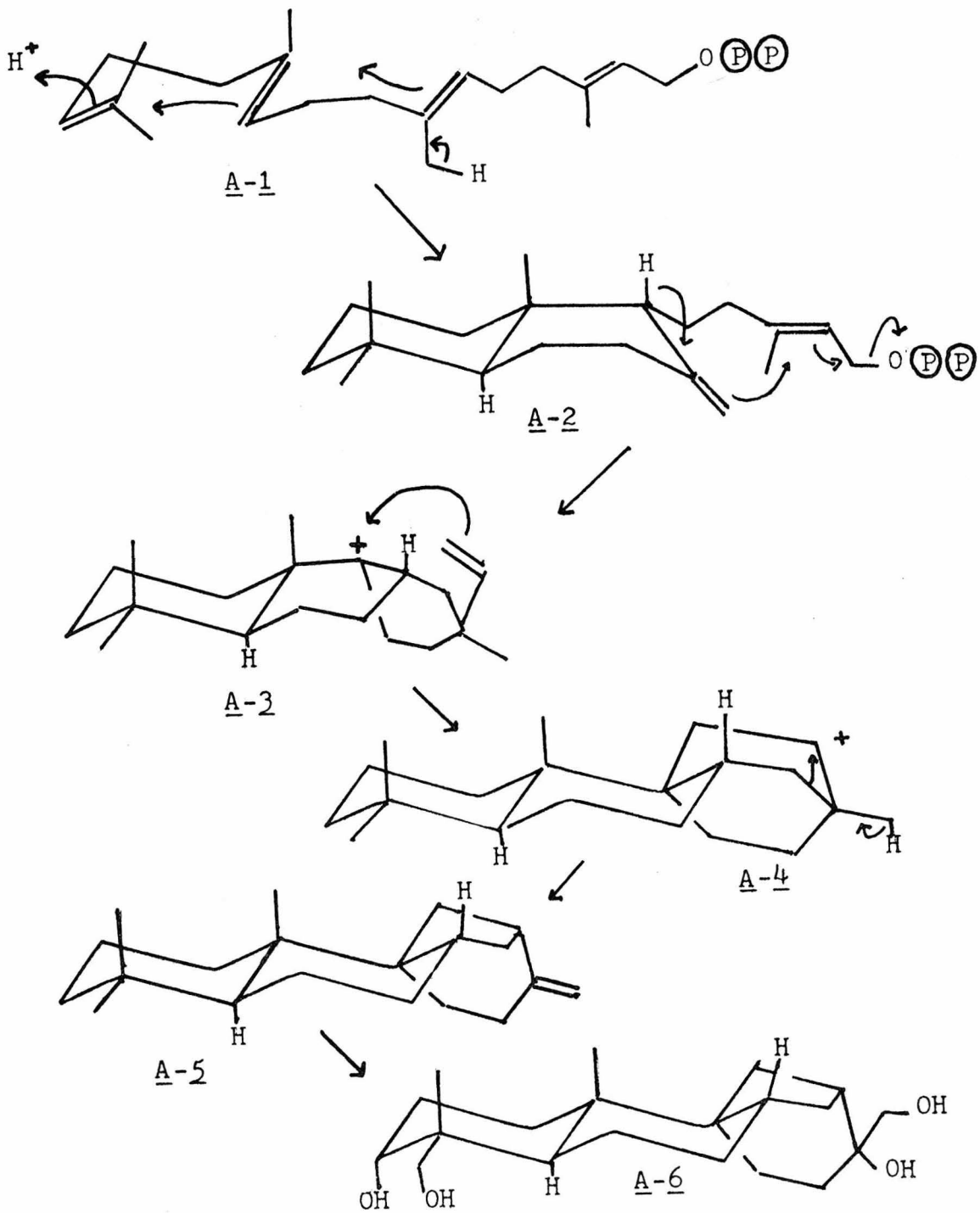
is much more potent than idoxuridine, it inhibits the growth of any idoxuridine-resistant herpesvirus, and does not appear to lead to development of any aphidicolin-resistant herpesvirus.

However, the effectiveness of aphidicolin is limited by its solubility in water, and efforts to increase water solubility caused a decrease in potency (10). Another problem with aphidicolin is that it is not specific for virus-directed DNA synthesis. The concentration required to reduce herpesvirus growth by 50% in vitro is close to that which inhibits cellular DNA synthesis by 50% (10). Moreover, the mechanism of the inhibition of the viral DNA synthesis is not known. Hence, it would be helpful to synthesize various analogs and derivatives of aphidicolin, as well as aphidicolin itself.

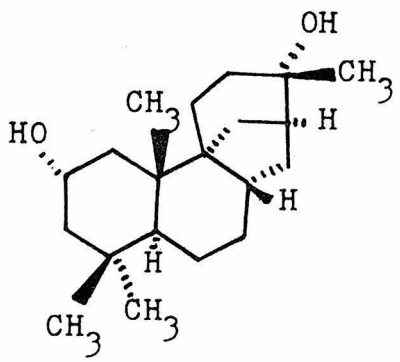
Recently, the biosynthesis of aphidicolin has been elucidated (12). As shown in Chart A, geranylgeranyl pyrophosphate (A-1) initially undergoes a chair-boat cyclization of the diterpene chain to furnish the bicyclic compound A-2. A hydride shift gives the pimaradiene

Chart A



cation A-3. Cyclization to compound A-4 followed by rearrangement furnishes aphidicolene (A-5). This novel cyclization of the pimaradiene cation and rearrangement was first suggested by Hesp (8). Aphidicolene is in fact found in culture filtrates of Cephalosporium aphidicola, and Hesp has suggested that aphidicolin (A-6) is formed by oxygenation of aphidicolene (8).

Shortly after the initial communication concerning the structure of aphidicolin appeared, two more members of this new class of diterpenes were reported by Manchand and White (13). They reported the isolation of the tetracyclic diterpenes stemodin (9) and stemodinone (10) from the leaves of the rare Jamaican flowering plant Stemodia maritima L (Scrophulariaceae). X-ray analysis again showed the six-membered rings in the chair conformation and the five-membered ring in an envelope conformation (13). Stemodin and stemodinone are epimeric with aphidicolin at C-9 and C-12 and also C-16 (aphidicolane



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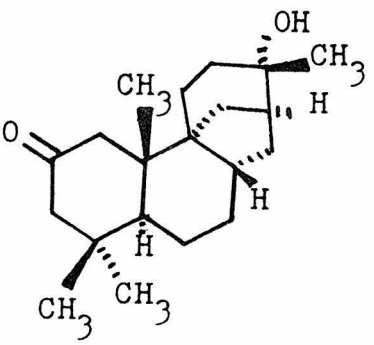

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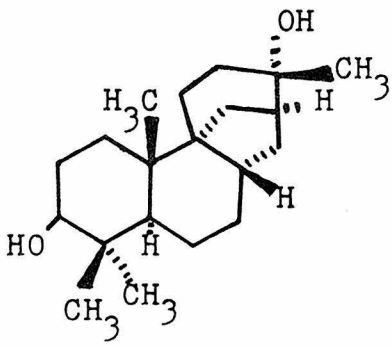
numbering). No biological activity for stemodin ($C_{20}H_{34}O_2$, m.p. 196-197°C, $[\alpha]_D$ -2.6° [c 1.07, pyridine]) or stemodinone ($C_{20}H_{32}O_2$, m.p. 215-216°C, $[\alpha]_D$ +14.3° [c 1.00, chloroform]) was reported.

Recently a more thorough investigation of Stemodia maritima has revealed two more diterpenes related to stemodin (14). Maritimol (11) ($C_{20}H_{34}O_2$, m.p. 169-170°C, $[\alpha]_D^{25}$ +3.7° [c 0.93, pyridine]) and stemodinol (12) ($C_{20}H_{34}O_2$, m.p. 182-183°C, $[\alpha]_D^{25}$ +13.8° [c 1.01, pyridine]) differ from stemodin and stemodinone only in the A ring (14). Note that in all four of these compounds the methyl group at C-17 (aphidicolane numbering) is equatorial so that the tertiary alcohol at C-16 is axial. In aphidicolin, the hydroxymethyl group at C-17 is equatorial and so the tertiary alcohol at C-16 is axial. Finally note that the hydroxymethyl group at C-18 in both aphidicolin and stemodinol is in the equatorial position.

The plant Stemodia maritima L (Scrophulariaceae) is used as a home remedy in the treatment of venereal



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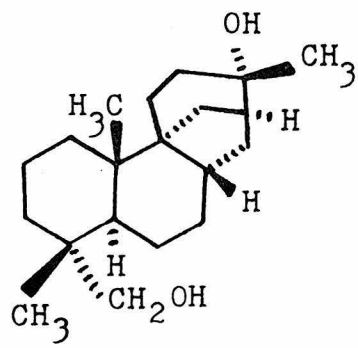

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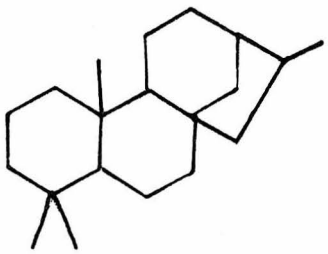
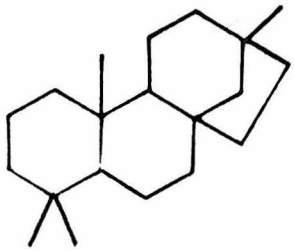
disease in the Carribean (14). Crude plant extracts showed antibacterial activity; however, no antiviral or antibacterial activity was attributed to stemodin, stemodinone, stemodinol, or maritimol (15). Aphidicolin, on the other hand, possesses antimitotic and antiviral activity against a wide range of DNA containing viruses, including the herpesvirus which is associated with venereal disease (10).

The skeletal structure of the aphidicolin class of diterpenes is dominated by the unusual bicyclo [3.2.1]-octane ring system. Other classes of diterpenes containing a bicyclo[3.2.1]octane ring system are shown in Chart B and include kaurane (B-1), stachane (B-2), gibbane (B-3), ericacane (B-4), and fujinane (B-5) skeletons (6). Each class possesses its own problems in synthesis (16). A bicyclo[3.2.1]octane skeleton is also found in one class of sesquiterpenes, the cedrane class (B-6) (17). The aphidicolin class is most closely related to the kaurene-phyllocladene series of tetracyclic diterpenes. However, in the aphidicolin series the six membered ring of the bicyclooctane is a spiro substituent on the decalin. Also, while in the aphidicolin class C-9 is quaternary and C-8 is tertiary, in the kaurane class the situation is just the opposite.

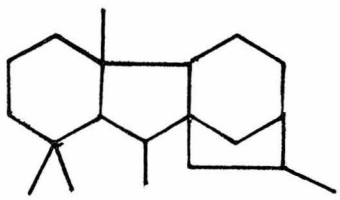
Chart B



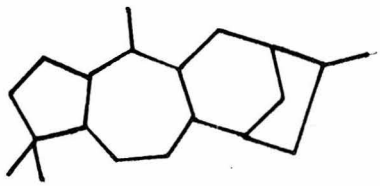
B-1



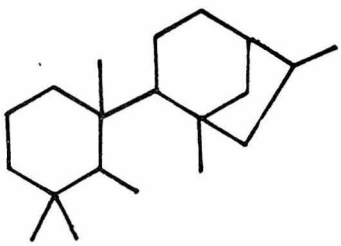
B-2



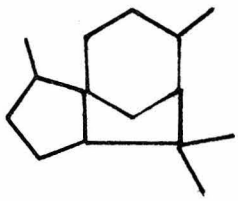
B-3



B-4



B-5



B-6

In any retrosynthetic analysis of aphidicolin it is clear that the main synthetic problem is the formation of the bicyclo[3.2.1]octane portion. Chart C illustrates several of the possible retrosynthetic paths available for aphidicolin. In path I the key carbon-carbon bond is formed in a classical aldol-type process. While paths III and IV represent efficient intramolecular solvolyses, path II utilizes some interesting photochemical reactions and acid catalyzed rearrangements.

Indian workers have in fact synthesized a stemodin model via path I (18). Their approach is illustrated in Chart D. Reduction of 6-methoxy-3′-oxo(2′,1′,1,2)cyclopentonapthalene (D-1) with sodium in ammonia followed by catalytic hydrogenation gave the ketone D-3 in 81% yield. Alkylation of ketone D-3 with 1-bromo-3,3-ethylenedioxypropane gave compound D-4 in 58% yield. This material now possesses the correct stereochemistry for the stemodin series and was converted to the bicyclo[3.2.1]octane system D-6 in 34% yield by deketalization followed by aldol condensation. Several subsequent steps converted this material into ketone D-8. While the yield in the cyclization step was disappointingly low, this still represents the first reported synthesis of the stemodin bicyclooctane skeleton.

Chart C

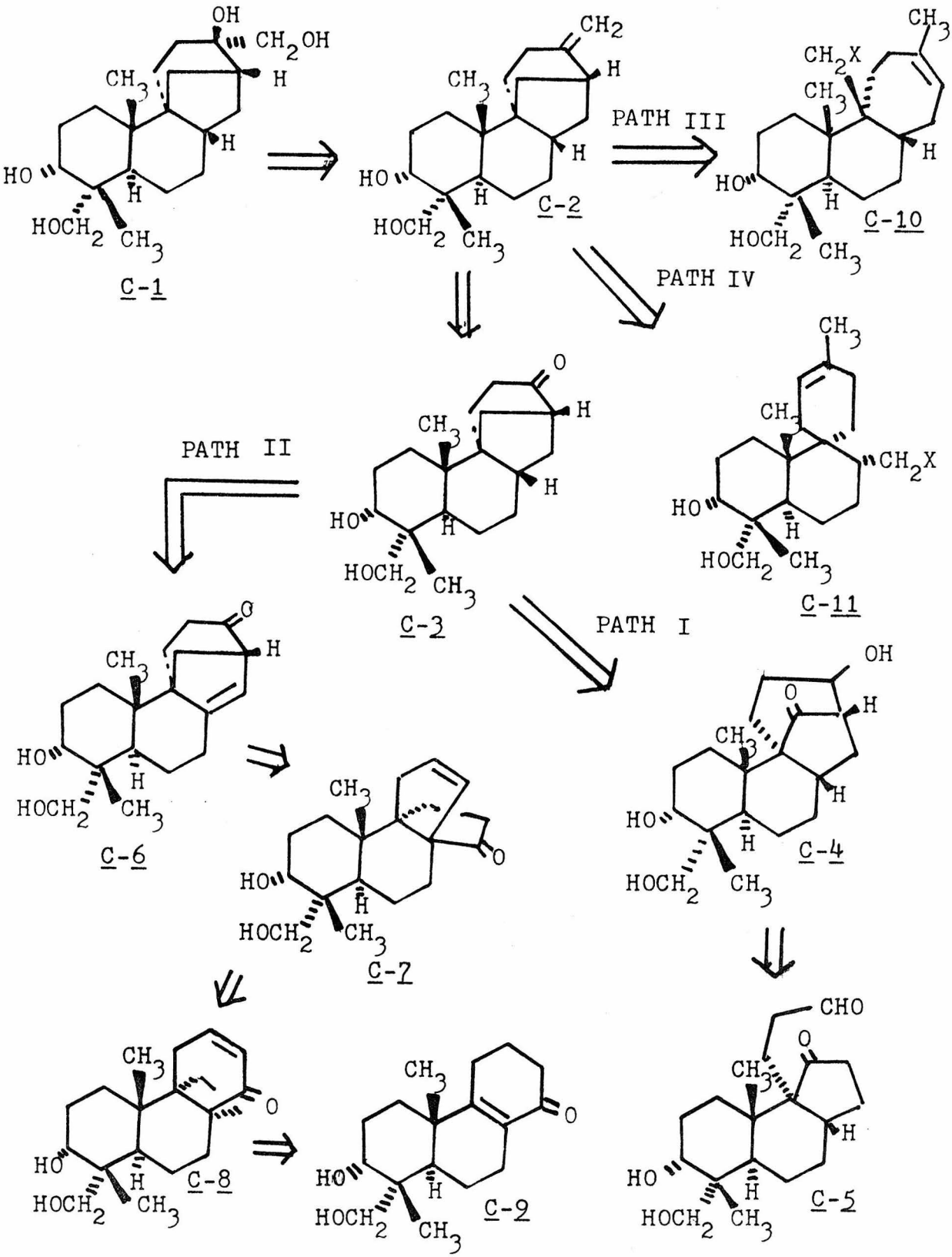
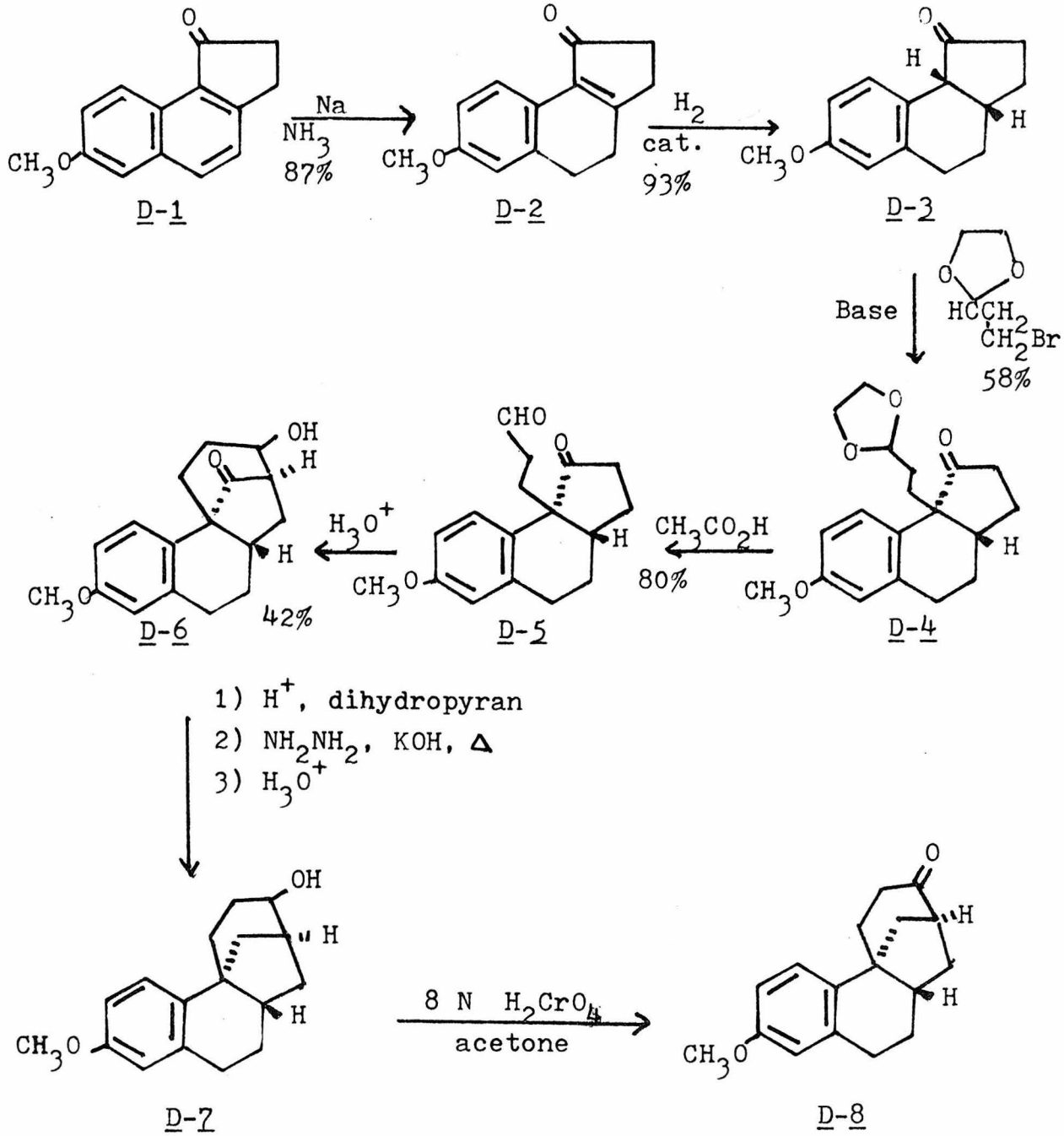


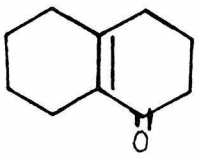
Chart D


Na
NH3
87%
H2
cat.
93%
Base
58%
CH3CO2H
80%
H3O+
42%
1) H+, dihydropyran
2) NH2NH2, KOH, Δ
3) H3O+
8 N H2CrO4
acetone
D-1
D-2
D-3
D-4
D-5
D-6
D-7
D-8

Path II in Chart C is a novel approach currently being pursued by Cargill and associates (19). Chart E illustrates their work in the model series (20). A photochemical [2+2] cycloaddition with ethylene and the enone E-1 furnishes the propellane E-2 in good yield. Introduction of the double bond by standard methods followed by treatment with an acid catalyst affords the rearrangement product E-4. Cargill has ample precedent for this type of rearrangement (21). Compound E-4 did not undergo a photochemical 1,3 acyl shift; however, the enone E-5 did give a one-to-one mixture of starting propellane E-5 and the desired tricyclic model E-6 (19).

Paths III and IV in Chart C both represent solvolyses with intramolecular participation by a remote double bond. Precedent for path III can be found in the work of Felkin and associates (22). Path IV was the route that was chosen by Ireland to synthesize aphidicolin. The key step involves the solvolysis of a primary leaving group (such as a tosylate) with participation by the double bond in the spiro ring. Corey (23) and Lawton (24) were able to synthesize the sesquiterpene cedrene (15) using such a biogenetic sequence.

Chart E

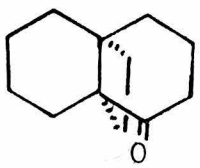


E-1

$h\nu$, $CH_2=CH_2$

CH_2Cl_2

84%



E-2

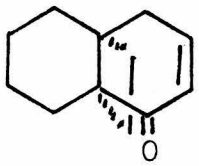
1) $LiN(i\text{-}Pr)_2$

2) Br_2

3) LiBr, DMF

Li_2CO_3

75%

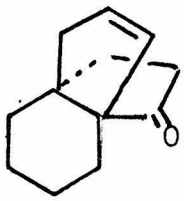


E-3

$BF_3 \cdot Et_2O$

C_6H_6, Δ

65%



E-4

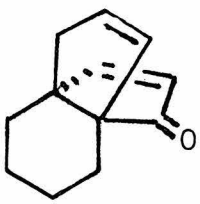
1) $LiN(i\text{-}Pr)_2$

2) C_6H_5SeBr

3) H_2O_2, CH_2Cl_2

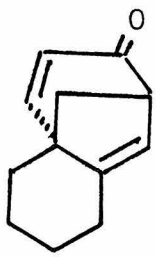
pryidine

12%

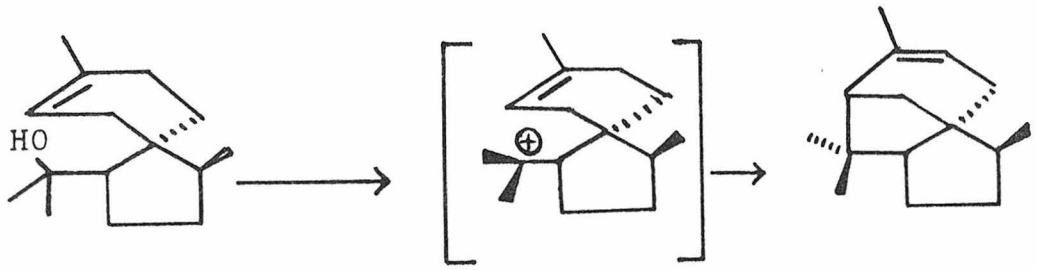


E-5

$h\nu$, hexane

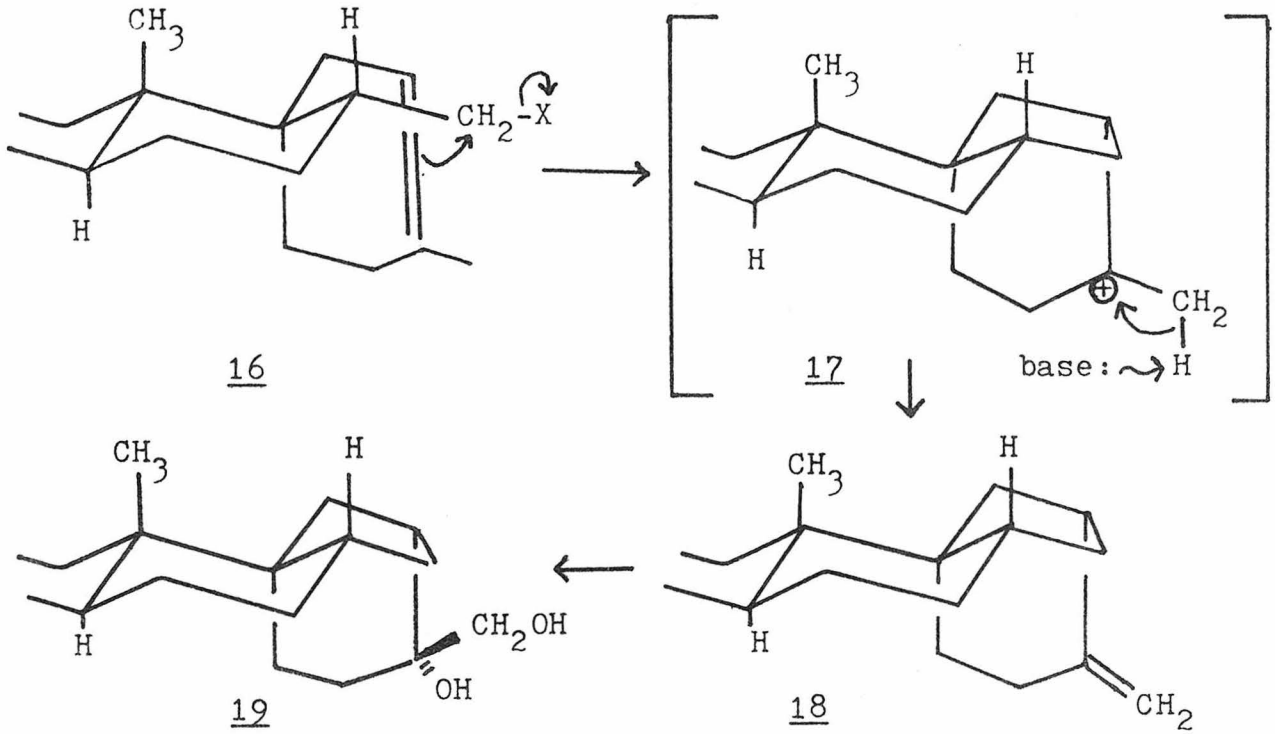


E-6



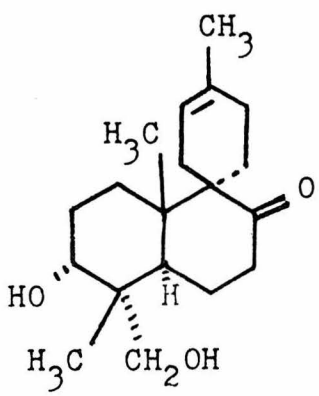
13 14 15

The precursor 16 of the bicyclooctane system in aphidicolin appears with Dreiding models to be ideally suited to such a solvolysis. Hydroxylation of the exo-olefin 18 with osmium tetroxide should then give the desired diol 19 for aphidicolin (attack from the least hindered face of the bicyclo[3.2.1]octane ring).

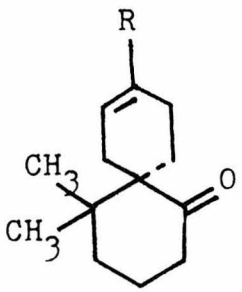


16 17 18 19

The solvolysis represented by path IV in Chart C requires the formation of a suitable spiro precursor such as compound 20. A large number of methods for constructing spiro systems are known (25, 26). One of the most direct methods to a spiro system such as model ketone 21 would be a Diels-Alder reaction with the ∝-methylene ketone 22. However, the reaction of compound 22 with 2-ethoxybuta-1,3-diene led to only a 20% yield of the desired product 21 (R=OCH_2CH_3) (27).



20



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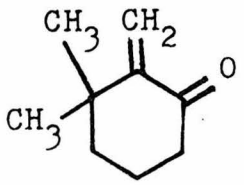
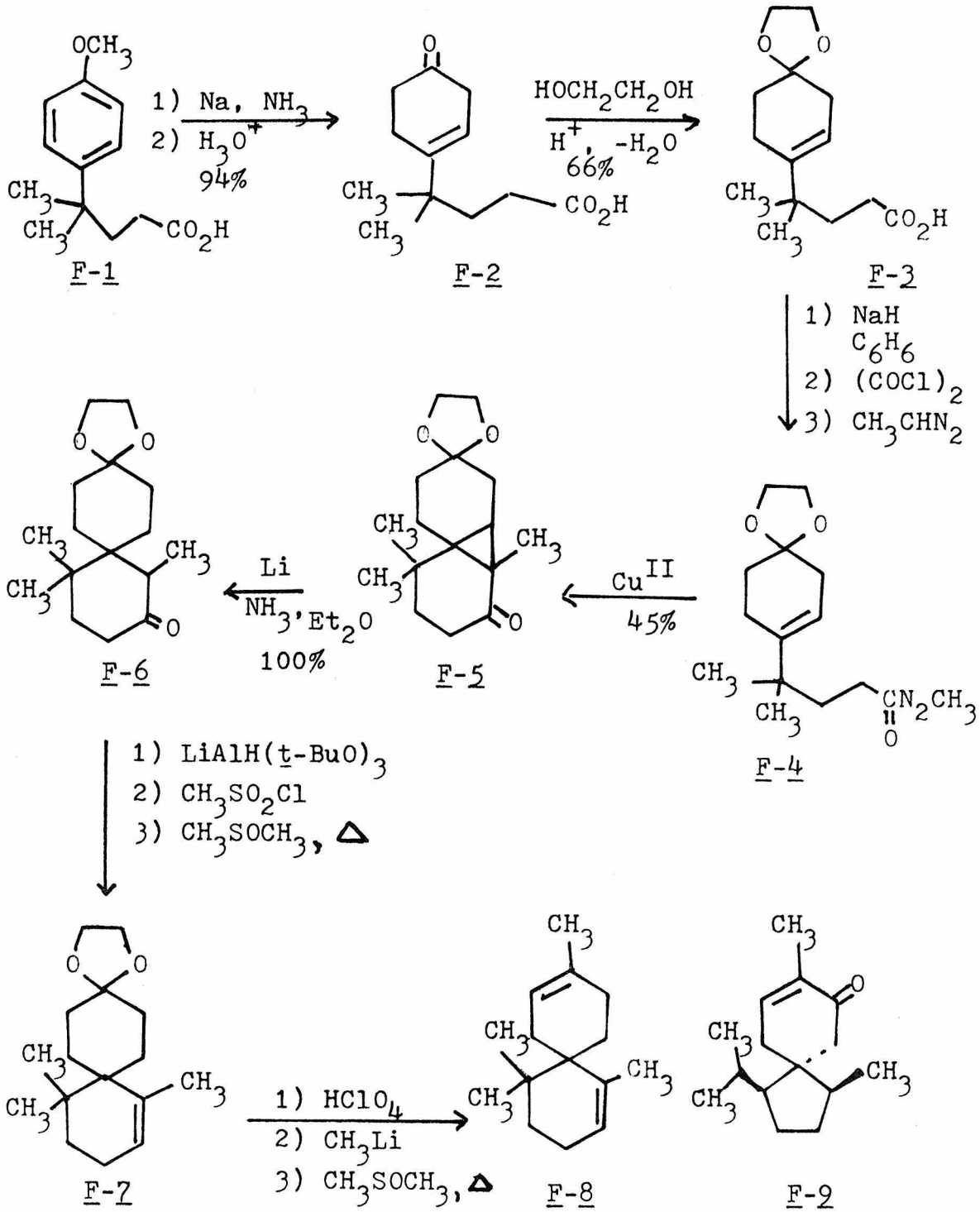


22

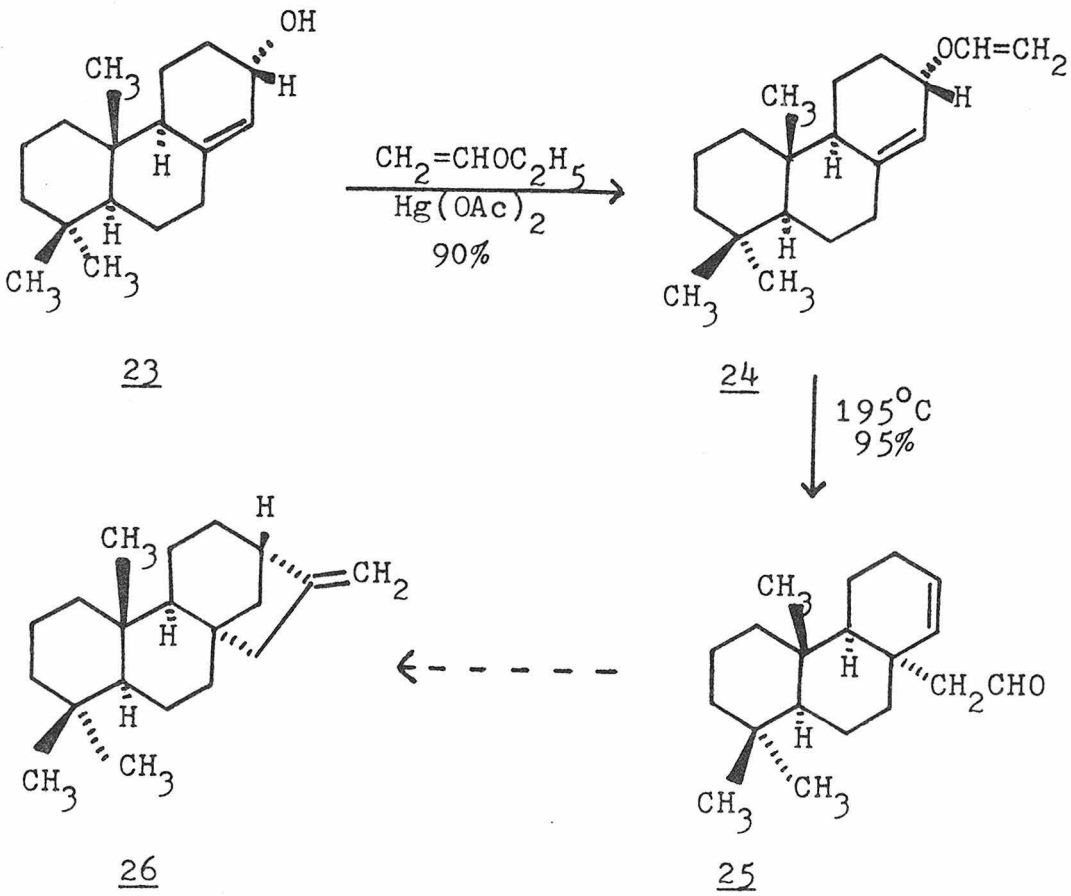
More recently White has reported a novel spiroannelation method involving an intramolecular addition of a diazoketone to an olefin followed by reductive cleavage of the resulting cyclopropyl ketone (28). Using this method, White was able to synthesize ∝-chamigrene (F-8) as shown in Chart F. The key step, addition of the diazoketone F-4 to the olefin using a copper catalyst,

Chart F


1) Na, NH3
2) H3O+
94%
HOCH2CH2OH
H+, -H2O
66%
1) NaH
C6H6
2) (COCl)2
3) CH3CHN2
CuII
45%
Li
NH3, Et2O
100%
1) LiAlH(t-BuO)3
2) CH3SO2Cl
3) CH3SOCH3, Δ
1) HClO4
2) CH3Li
3) CH3SOCH3, Δ
F-1
F-2
F-3
F-4
F-5
F-6
F-7
F-8
F-9

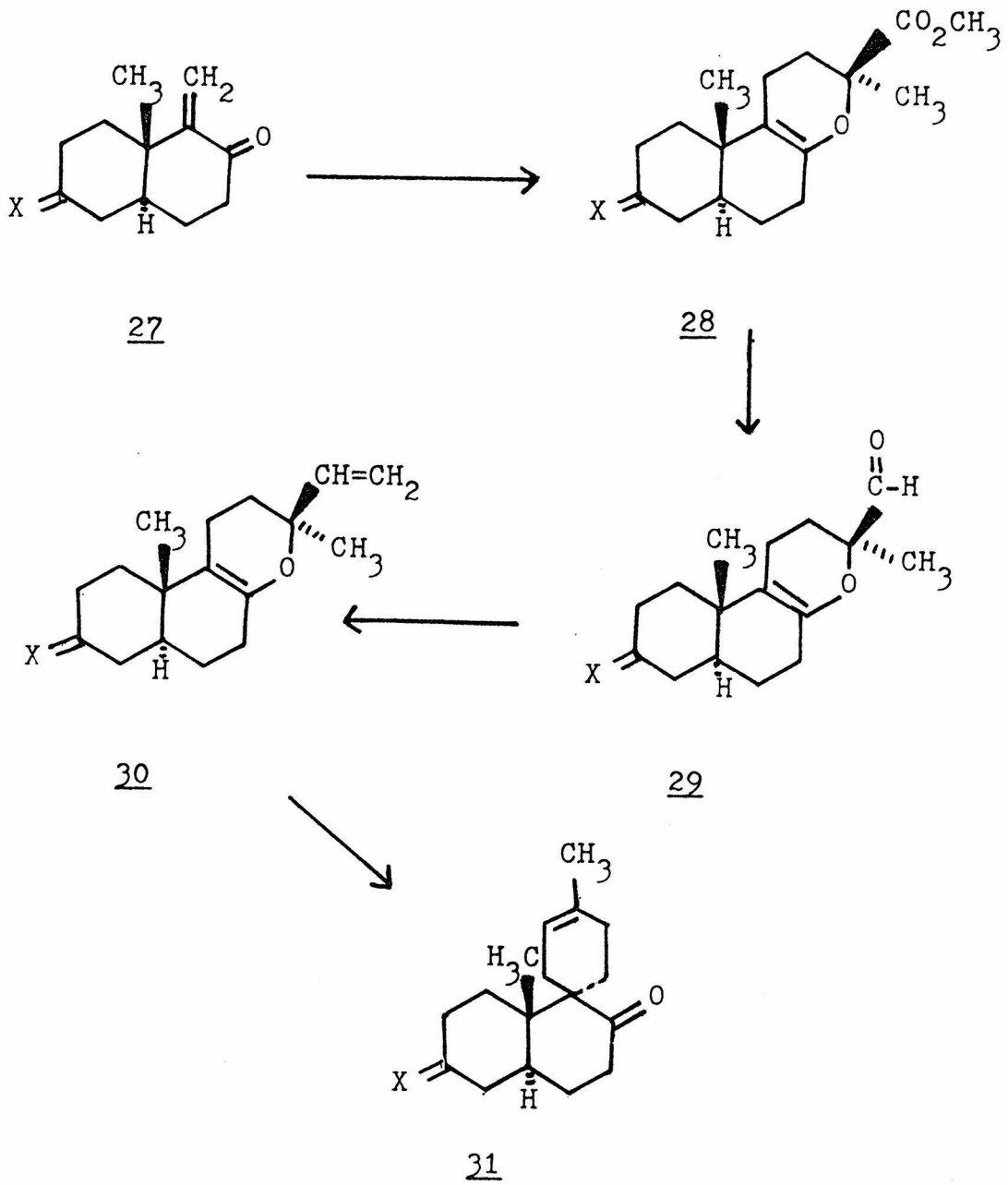
went in only modest yield, but the cleavage of the cyclopropyl ketone F-5 resulted in a quantitative yield of a precursor readily convertible to chamigrene. This type of spiroannelation has also been used to synthesize the sesquiterpene acorenone B (F-9) (29).

The approach Ireland planned to use was a new type of spiroannelation in which the key step would be a Claisen rearrangement. The Claisen rearrangement is no stranger to the Ireland laboratories. For example, more than ten years ago it was used in the synthesis of kaurene (26) (30,5).



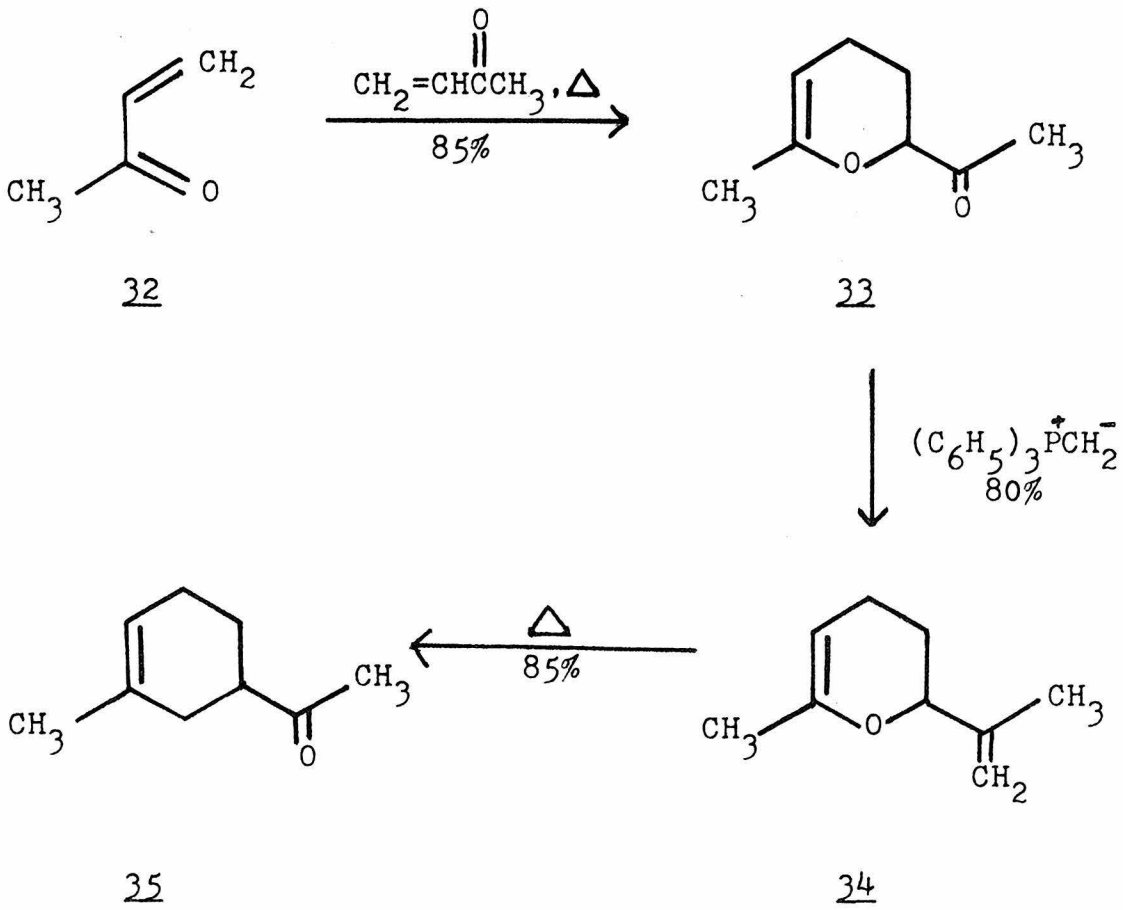
23 24 25 26

The plan for aphidicolin was to perform a Diels-Alder reaction on the methylene ketone 27 with methyl methacrylate, reduce to give the aldehyde 29, use a Wittig reaction to give the olefin 30, then thermally rearrange to make the spiro ketone 31.



27 28 29 30 31

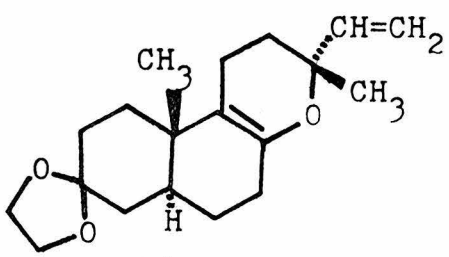
Literature precedent for such a sequence has been reported by Büchi (31). Büchi presented the method shown below as a new synthesis of cyclohexenes and indicated that the Claisen rearrangement probably was going through a boat-like transition state, contrary to most Claisen or Cope rearrangements. The initial Diels-Alder reaction between the α,β-unsaturated ketone (or α,β-unsaturated ester) and the methylene ketone (such as 32 or 27) is known to be completely regiospecific. Theoretical treatments show that this should be the case (32, 33).



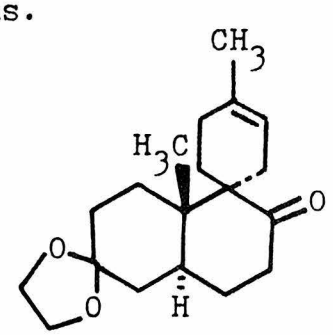
32 33

35 34

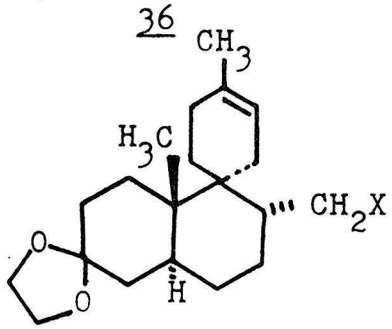
The feasibility of the Ireland approach to aphidicolin was first tested in a synthesis of ∝-chamigrene by Farr (34). His results are shown in Chart G. These preliminary results looked promising so it was decided to approach aphidicolin via this novel type of spiroannelation. The initial retrosynthetic analysis of aphidicolin is shown in Chart H. Since the Diels-Alder reaction on the methylene ketone H-8 will probably give an epimeric mixture of esters, resulting in an epimeric mixture of olefins (H-7 and 36), there will be two Claisen products produced (H-6 and 37). Solvolysis of compound 38 would then lead to tetracyclic compound 39, a key intermediate in the stemodin series. Hence, the initial proposed synthesis was versatile enough to allow for the construction of both the aphidicolin and stemodin ring systems.



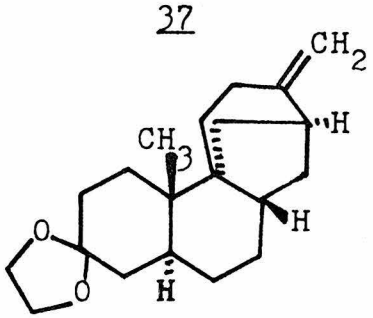
36



37



38



39

Chart G

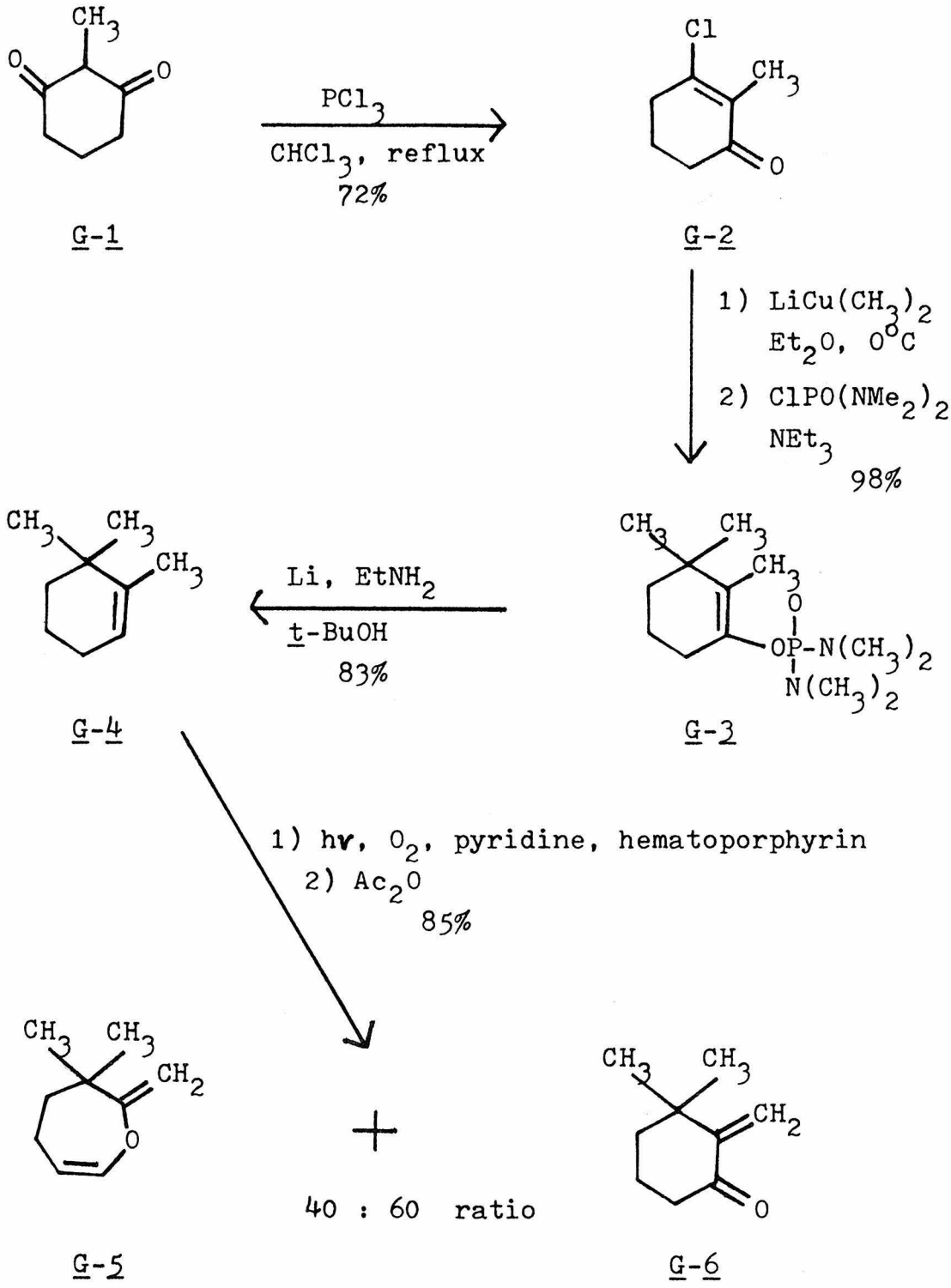

CH3
O
O
PCl3
CHCl3, reflux
72%
Cl
CH3
O
G-1
G-2
1) LiCu(CH3)2
Et2O, 0°C
2) ClPO(NMe2)2
NEt3
98%
CH3
CH3
CH3
O
OP-N(CH3)2
N(CH3)2
Li, EtNH2
t-BuOH
83%
G-4
G-3
1) hν, O2, pyridine, hematoporphyrin
2) Ac2O
85%
CH2
O
+
40 : 60 ratio
G-5
G-6

Chart G (continued)

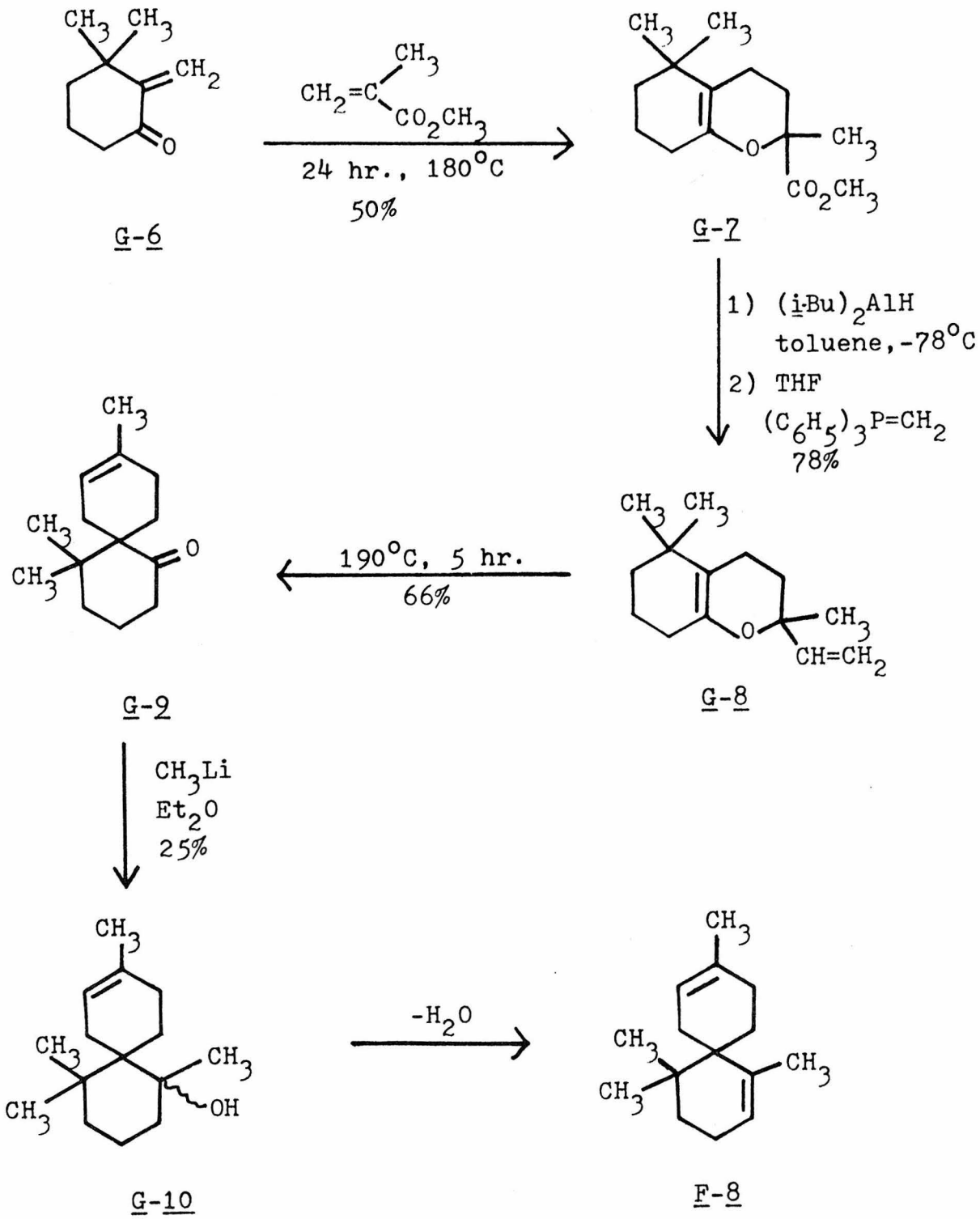
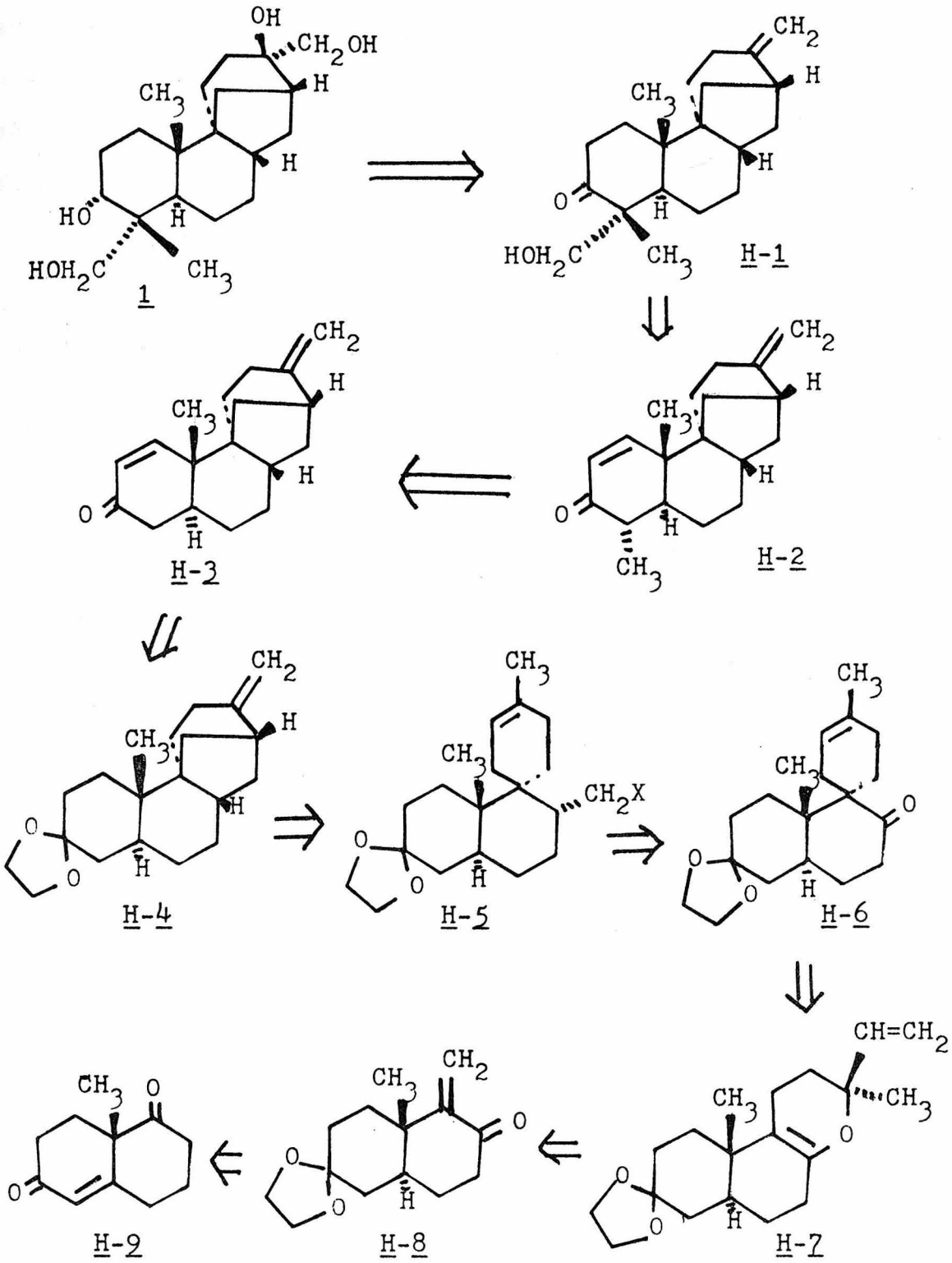


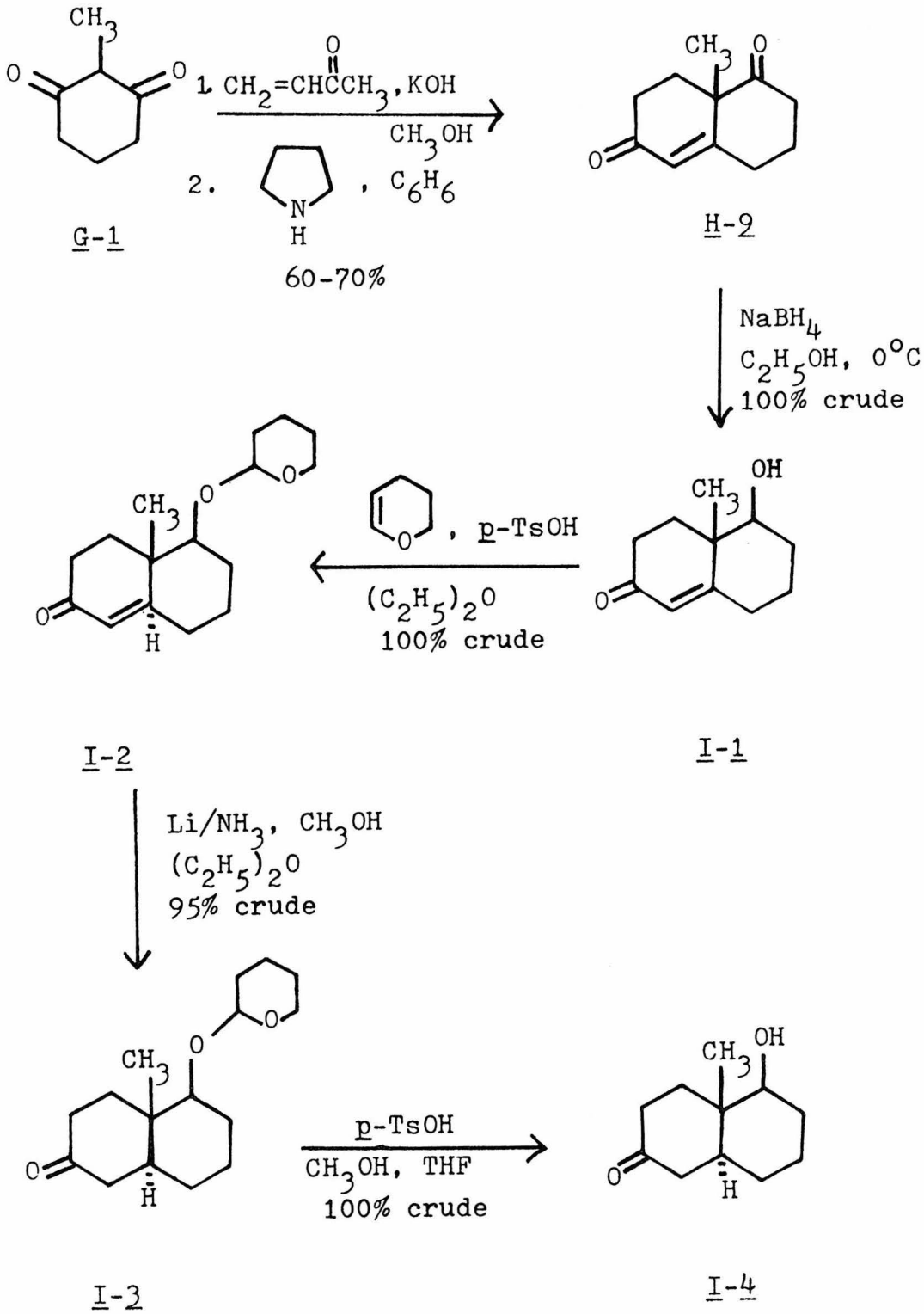
Chart H


OH
CH2OH
CH3
H
HO
HOH2C
CH3
1
CH2
H-1
H-2
H-3
H-4
CH2X
H-5
H-6
CH=CH2
H-7
H-8
H-9

The starting methylene ketone H-8 was available in ten steps from Wieland-Miescher ketone (H-9) with an overall yield of about 30% (35). This synthesis, developed in the Ireland group and used in a number of projects including an approach to fusidic acid, is shown in Chart I (36).

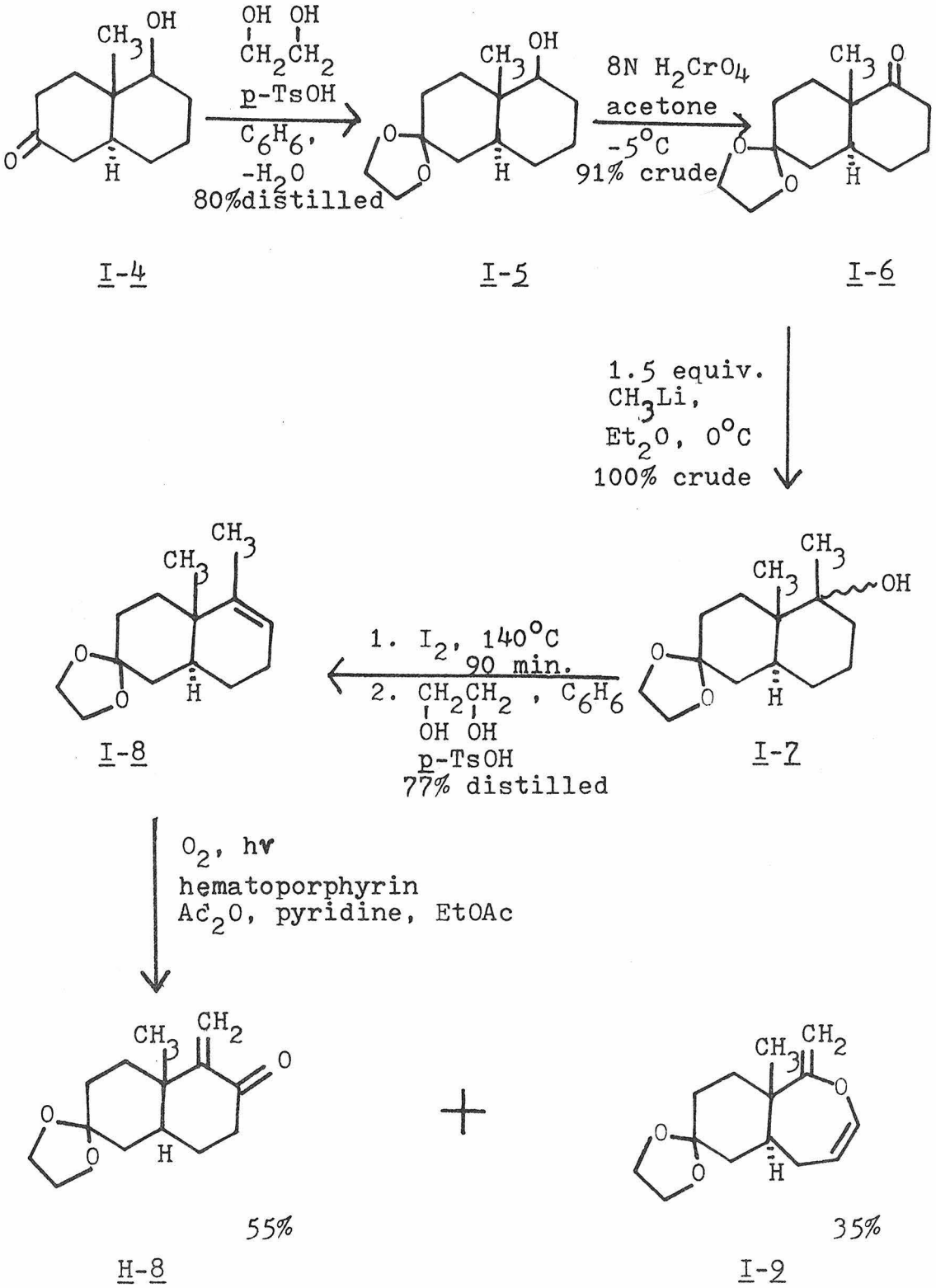
The synthetic intermediates discussed in this thesis are all racemic. For convenience, only one enantiomer has been depicted in the structural formulas.

Chart I



G-1 H-2 I-1 I-2 I-3 I-4

Chart I (continued)



I-4 I-5 I-6

I-8 I-7

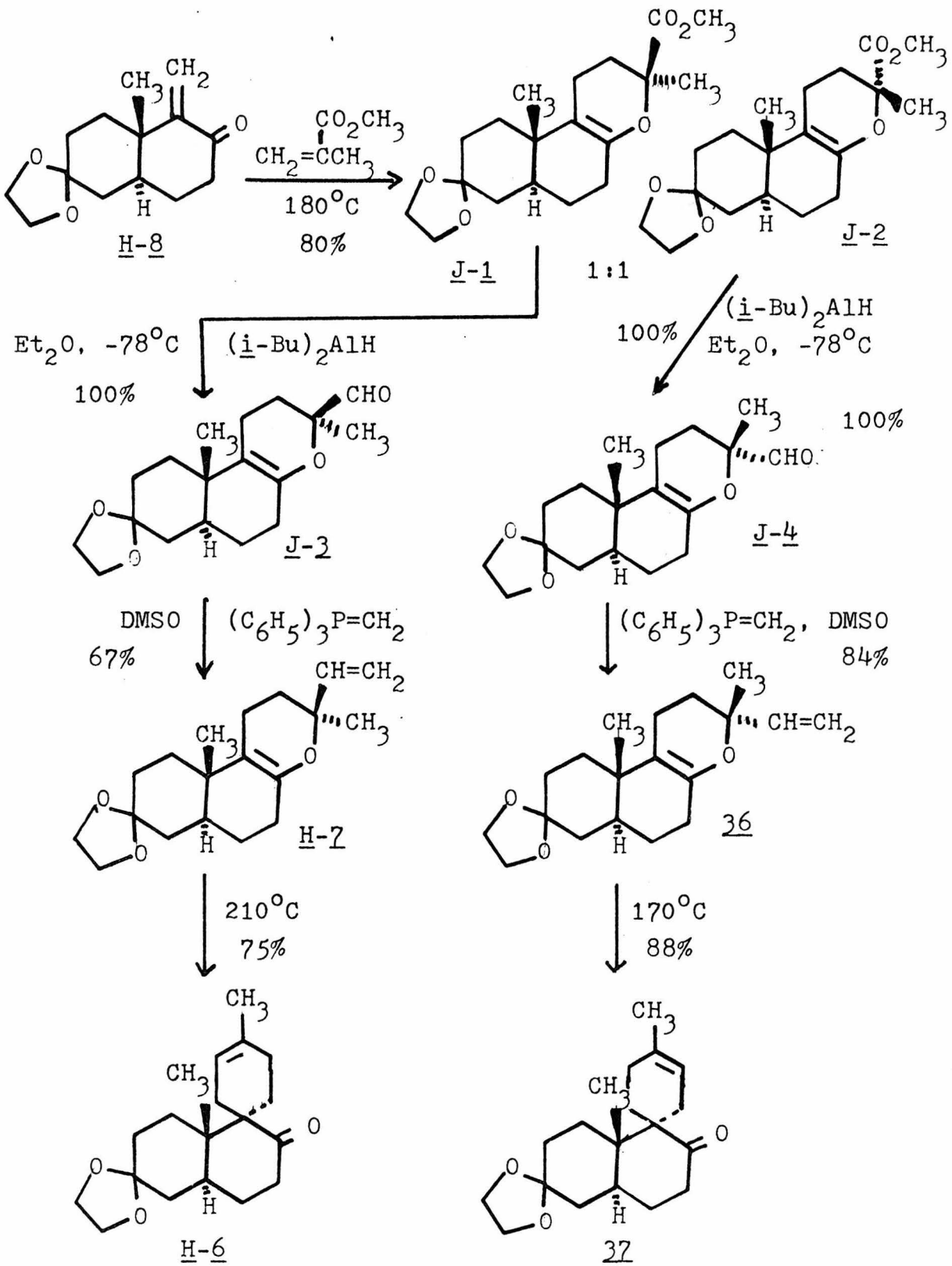
H-8 I-9

Discussion

The initial goal was to synthesize the spiro ketone H-6. As illustrated in Chart J, methylene ketone H-8 and methylmethacrylate were heated in a sealed tube at 180°C for 22 hours to give 80% yield of about a one-to-one mixture of Diels-Alder adducts J-1 and J-2 which are epimeric at C-13 (steroid numbering). The two compounds could be separated by chromatography at this stage and reduced with diisobutylaluminum hydride in ether at -78°C to give a quantitative crude yield of the corresponding aldehydes. A normal Wittig reaction was performed in dimethylsulfoxide at room temperature on the aldehydes J-3 and J-4 to give the olefins H-7 (67% yield over two steps) and 36 (84% yield over two steps). The Claisen reaction on olefin H-7 was performed for one hour at 210°C in a base washed sealed tube to give 75% chromatographed yield of spiro ketone H-6, while the Claisen rearrangement of olefin 36 proceeded for one hour at 170°C to give an 88% yield of the spiro ketone 37.

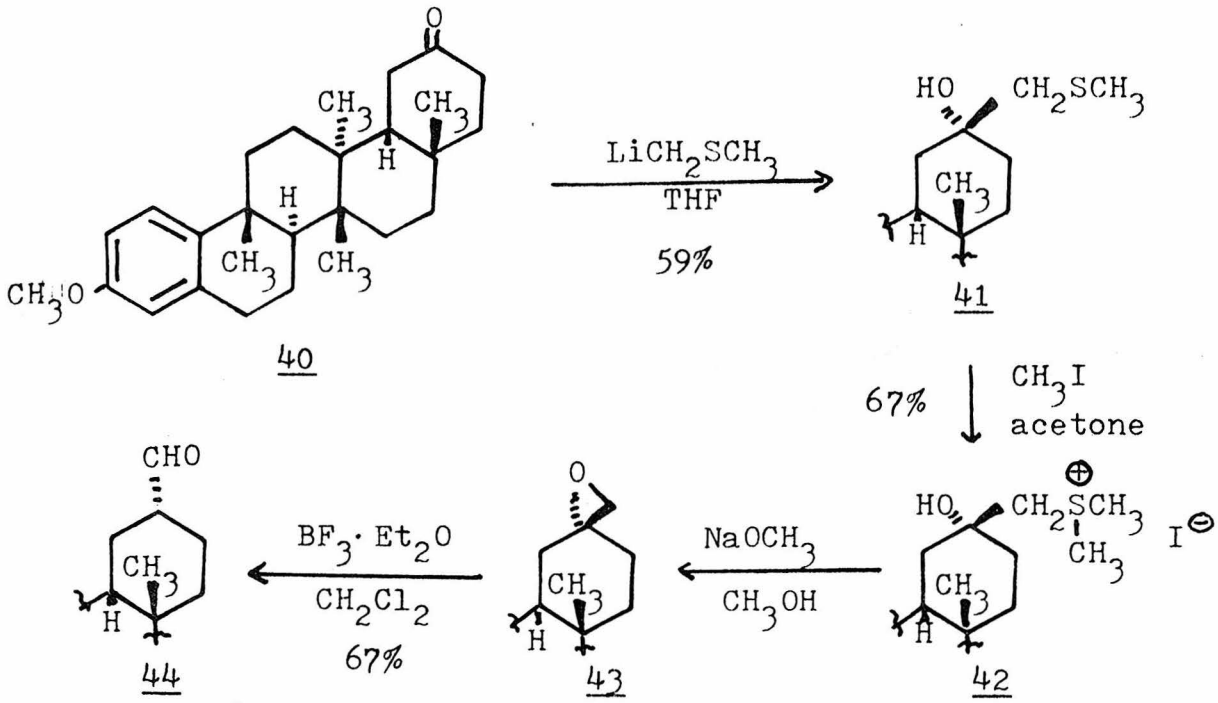
There were several reasons for the proposed assignment on configuration to the esters J-1 and J-2. A lanthanide shift study was first done which indicated that compound J-1 was the β-ester and compound J-2, the α-ester. Also compound J-1 was eluted before compound J-2 indicating that it was the hindered pseudoaxial ester.

Chart J


H-8
CH2=CCH3
CO2CH3
180°C
80%
J-1
1:1
J-2
Et2O, -78°C
(i-Bu)2AlH
100%
J-3
100%
J-4
DMSO
67%
(C6H5)3P=CH2
H-7
(C6H5)3P=CH2, DMSO
84%
36
210°C
75%
170°C
88%
H-6
37

Moreover, compound J-1 was harder to reduce with diisobutylaluminum hydride. Stronger evidence for the assignment of configuration was in the thermal Claisen rearrangement. While compound 36 gave 88% yield of spiro ketone 37 when heated for one hour at 170°C, olefin H-7 gave only 10% yield of compound H-6 and 80% yield of starting material under similar conditions. It was necessary to heat olefin H-7 for one hour at 210°C to get a good yield of spiro ketone H-6. The reason for this difference in activation energies could be that compound H-7 has the monosubstituted olefin beta as shown so that the angular methyl group at C-10 exhibits considerable steric hindrance towards the topside approach of this olefin in the Claisen rearrangement. Backside approach with olefin 36 is not hindered and the rearrangement proceeds at a lower temperature.

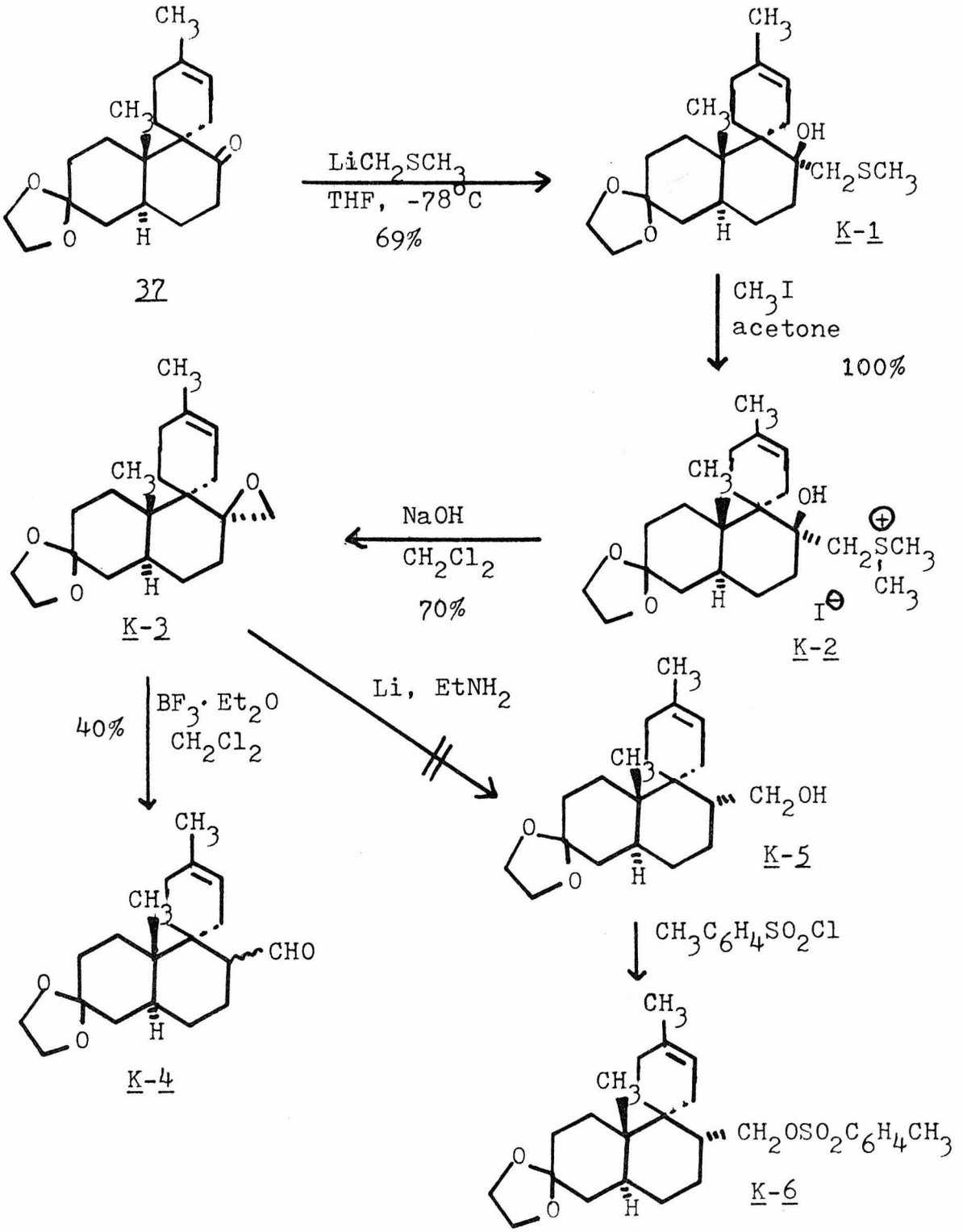
Now the problem was to add a functionalized methyl group to the ketone at C-8. However, it is known that this position is very hindered. In the α-chamigrene synthesis, addition of methyllithium to ketone G-9 at -78°C gave 25% yield of alcohol G-10 and 75% starting material (34). Evidently enolization is kinetically favored over addition to the hindered carbonyl. In compounds H-6 and 37 the steric problem is even more serious. An attempt to overcome this problem was made by using the method of Johnson and Coates in which the extremely nucleophilic anion of



dimethylsulfide is employed in the addition to a hindered or readily enolizable ketone (37). One example of the use of this reagent in an approach to alnusenone is shown above (38). Compounds such as di-t-butylketone and deoxybenzoin have been alkylated in nearly quantitative yields by this procedure (37). If ketones H-6 and 37 could be converted to aldehydes in a similar manner, then the aldehydes could be equilibrated to the desired equatorial isomers, reduced to primary alcohols and tosylated to give the key intermediates L-2 and K-6.

Accordingly, the synthetic scheme shown in Chart K was undertaken. Alcohol K-1 was obtained in 69% yield (plus 21% starting material) by the addition of ketone 37

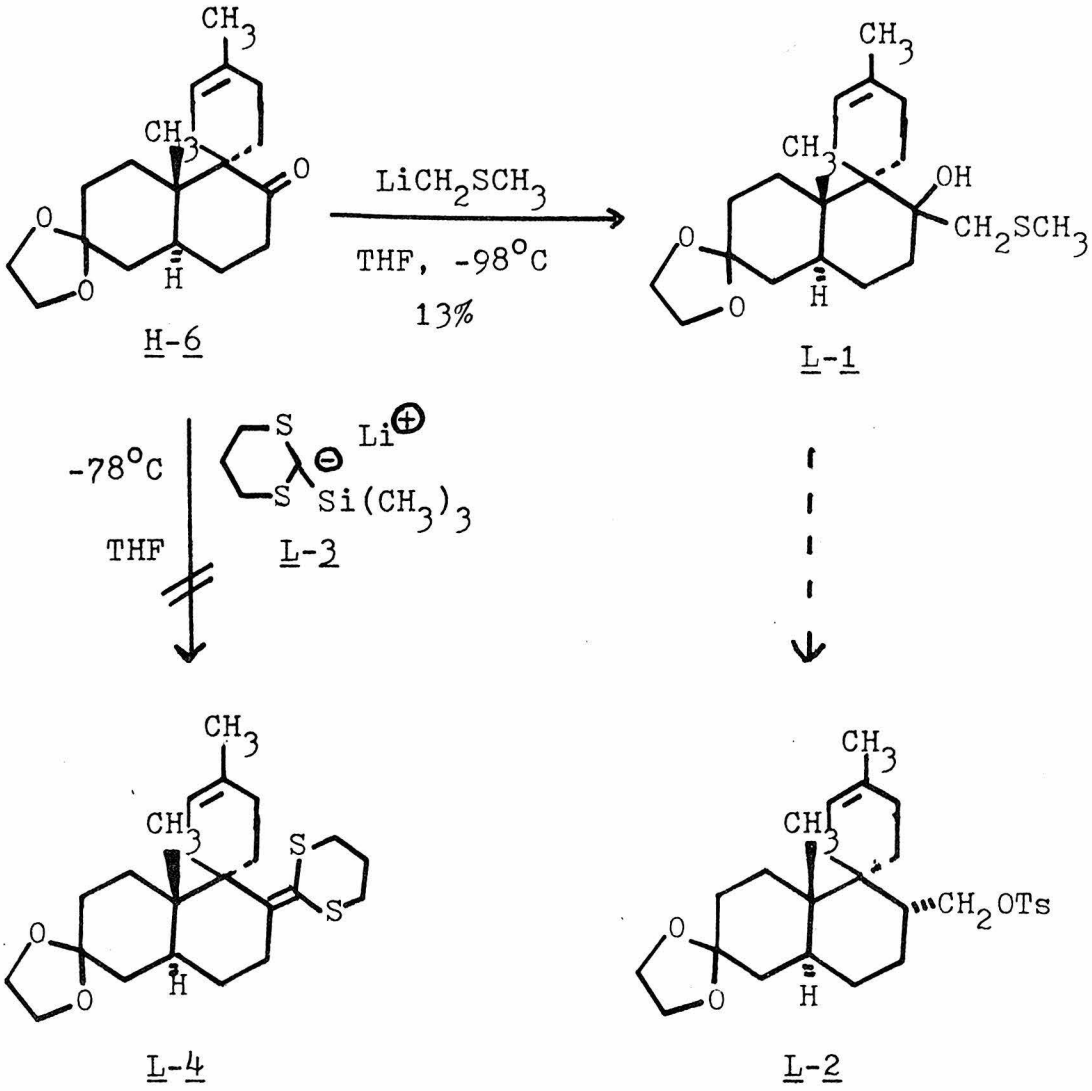
Chart K


CH3
CH3
O
O
O
H
37
LiCH2SCH3
THF, -78°C
69%
OH
CH2SCH3
K-1
CH3I
acetone
100%
⊕
CH2SCH3
CH3
I⊖
K-2
NaOH
CH2Cl2
70%
K-3
Li, EtNH2
40%
BF3·Et2O
CH2Cl2
CHO
K-4
CH2OH
K-5
CH3C6H4SO2Cl
CH2OSO2C6H4CH3
K-6

to four equivalents of the anion of dimethyl sulfide in tetrahydrofuran at -78°C. The sulfide K-1 was alkylated by stirring at room temperature with four hundred equivalents of methyl iodide in acetone for forty-eight hours. The crude salt K-2 was then stirred overnight at room temperature in the two phase system of methylene chloride and fifteen equivalents of 0.5 N aqueous sodium hydroxide to give 70% chromatographed yield (over two steps) of the epoxide K-3. The stereochemistry of the epoxide is probably as shown because the lithium dimethyl sulfide anion should attack compound 37 preferentially from the less hindered alpha face of the ketone. An attempt to form the epoxide K-3 directly from the ketone 37 using dimethyloxosulfonium methylide (39) afforded only unchanged starting material.

A further argument for the configuration of the two esters J-1 and J-2 was from the results of the addition of nucleophiles to the spiro ketones 37 and H-6 (Charts K and L). While compound 37 could be alkylated in 50-70% yield with the nucleophilic, relatively non-basic anion of dimethyl sulfide (37), compound H-6 was alkylated with a maximum of 13% yield under similar conditions. One possible reason for this discrepancy in yields is indicated as follows. Topside attack of compound 45 (37) is hindered by the angular methyl at C-10. However, approach from the alpha face is much less hindered so attack by $LiCH_2SCH_3$

Chart L



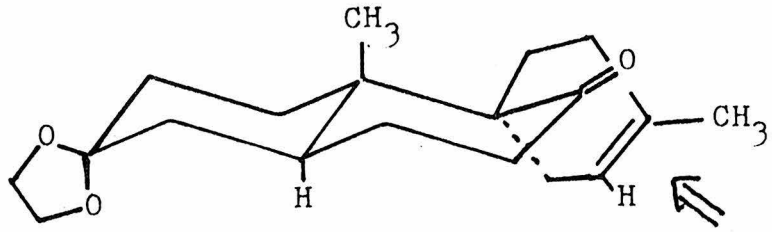
H-6

L-1

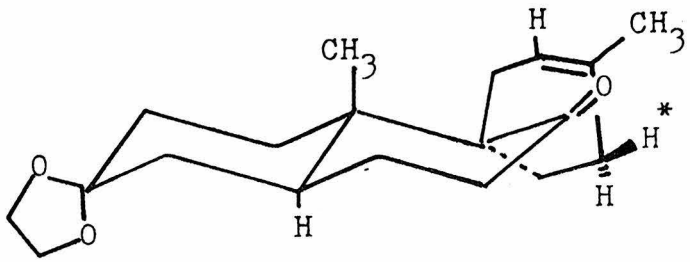
L-3

L-4

L-2



45



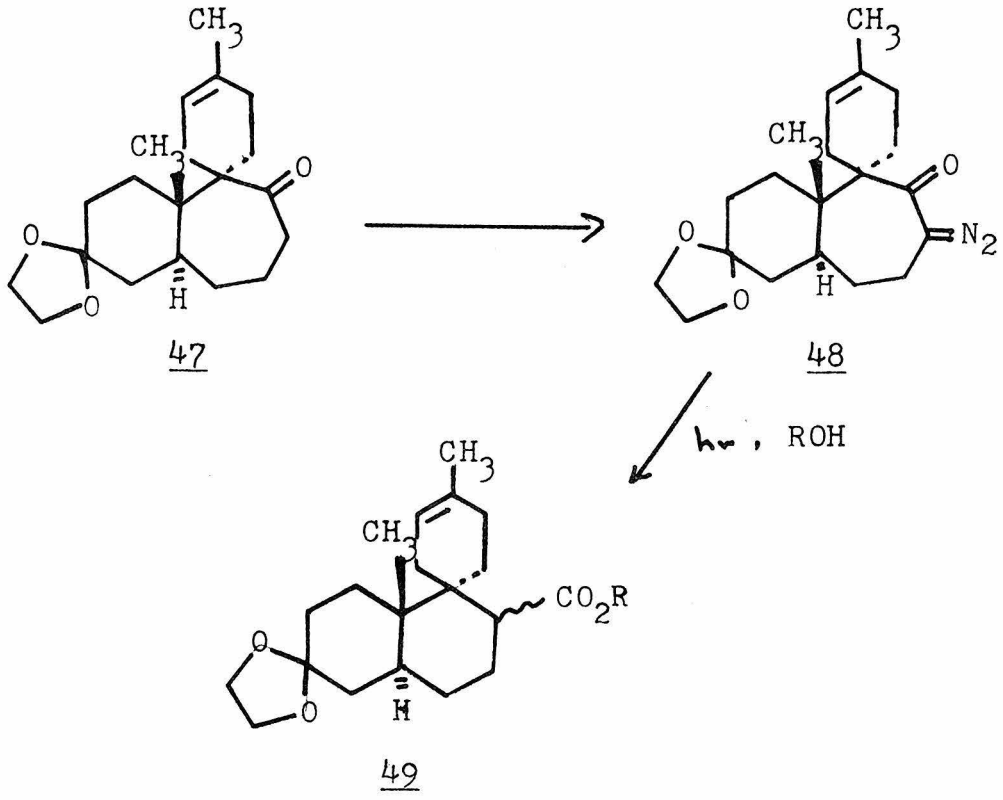
46

probably occurs from this side as shown above (see also Chart K). However, in compound 46 (H-6) both sides of the ketone are hindered. The beta side, as before, has the steric hindrance of the angular methyl group, but now backside attack of the ketone is hindered by the starred hydrogen (in 46) which was not present in compound 45.

Attempts at reducing or rearranging the epoxide K-3 were not very successful. The yield of aldehyde K-4 (obtained by rearrangement of epoxide K-3 with boron trifluoride etherate in methylene chloride at -25°C) was 40% to 50%; another 30% to 40% was a solid compound whose spectra indicated that skeletal rearrangement had taken place. Reduction of the epoxide with lithium in ethylamine (or ethylenediamine) and tertiary butyl alcohol (40)

again led to a mixture of products showing that skeletal rearrangement had taken place.

A more serious problem with this route was that treatment of compound H-6 in Chart L with lithium dimethyl sulfide anion gave only 13% alkylated material L-1 and 80% starting material. Even the addition of the dithiane anion L-3 (41) to ketone H-6 gave only recovered starting material. Since compound H-6 is the precursor for aphidicolin, a better method for introducing the one carbon group with appropriate functionality was clearly needed. The other problems associated with the epoxide K-3 also indicated a new route was necessary. Accordingly, an intramolecular scheme (shown below) was chosen to introduce

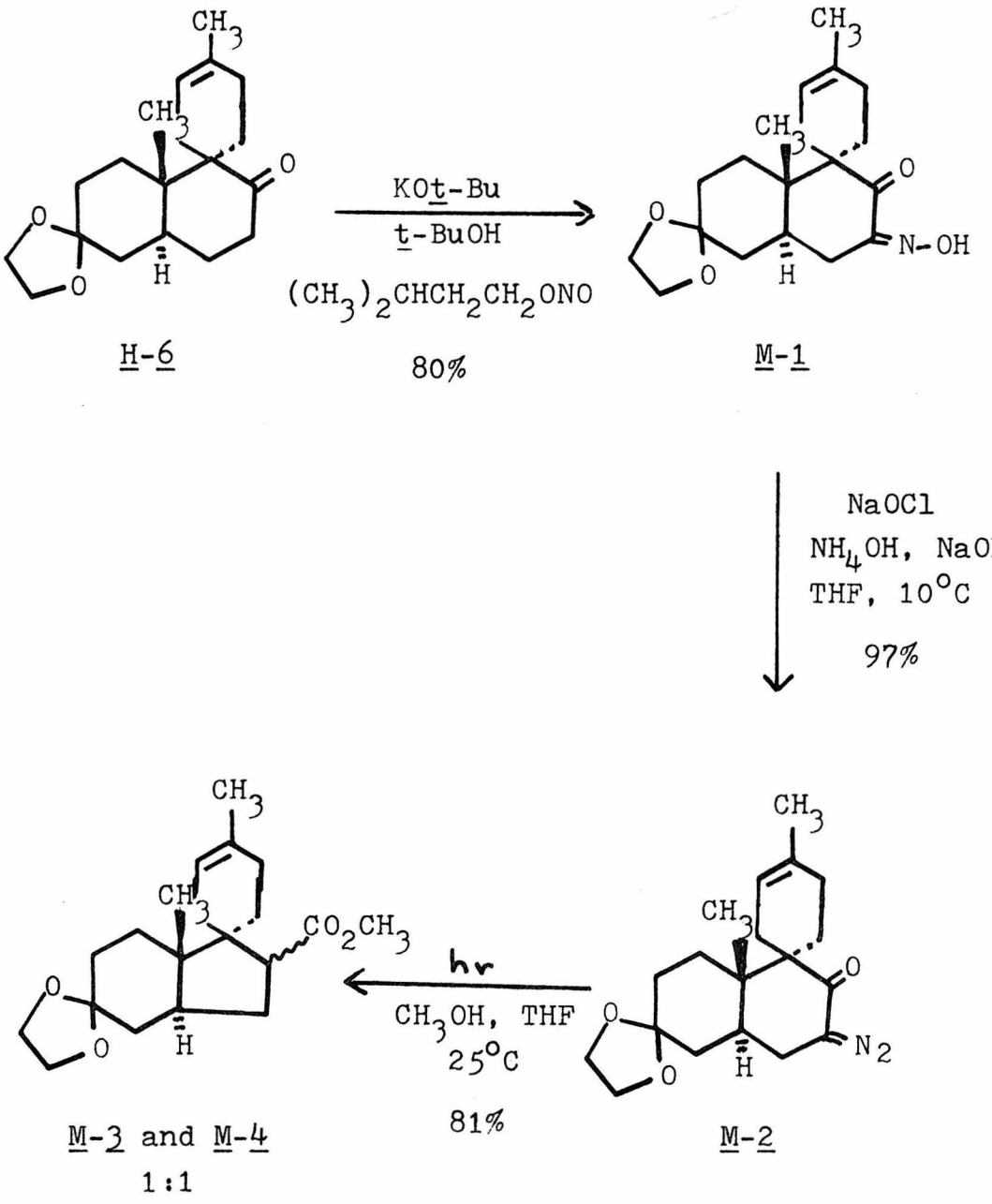


the carbon unit at C-8 of the spiro ketone. Cava (42) and Meinwald (43) used just such a Wolff rearrangement to produce D-norsteroids.

The reactions were attempted successfully on the model system H-6 as shown in Chart M. The ketone H-6 upon treatment with one equivalent of base and one equivalent of isoamyl nitrite in tertiary butyl alcohol afforded a high yield of the oximo ketone M-1. The diazo ketone was prepared in 97% crude yield from mixing the ketone M-1 with chloramine (prepared from sodium hypochlorite, sodium hydroxide, and ammonium hydroxide) at 10°C in tetrahydrofuran. The photolysis of the diazo ketone M-2 was performed in tetrahydrofuran at room temperature with a Hanovia medium pressure mercury vapor lamp in a quartz immersion well with a pyrex filter. With methanol as cosolvent the desired esters M-3 and M-4 (epimeric at C-7) were produced in 81% yield in about a one-to-one mixture.

In the synthesis of aphidicolin, ring contraction would be from a seven-membered ring to a six-membered ring, an even more favored process. This synthetic scheme represents a method of modifying spiro compounds to introduce an alkyl group at the hindered position alpha to the spiro ring. This sequence seemed to be an improvement over the sequences in Charts K and L.

Chart M



H-6

M-1

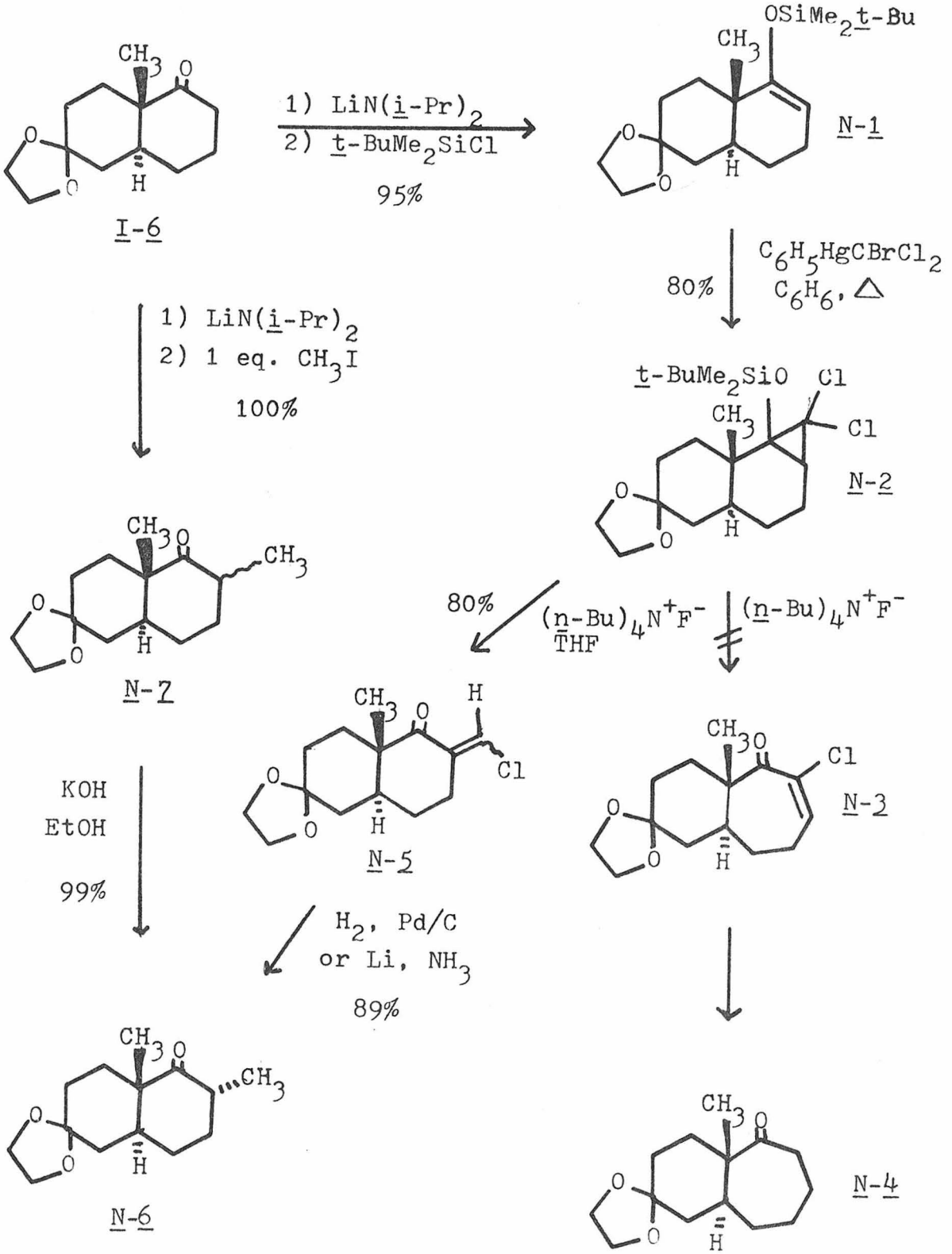
M-2

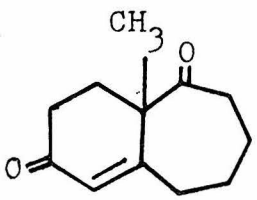
M-3 and M-4

1:1

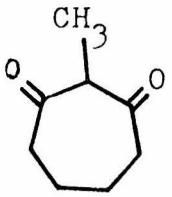
Since a large quantity (about 120 grams) of the intermediate I-6 was available, the initial plan was to expand this ketone to the seven-membered ring ketone N-4, and then pursue the synthesis of spiro ketone 47 along the lines of Charts I and J. Stork's procedure (44) appeared to be ideal for this type of ring expansion since it was reported to be completely regiospecific and it did not involve any acidic conditions (which would have destroyed the ketal). Accordingly, the silyl enol ether N-1 was refluxed in benzene with two equivalents of Seyferth's reagent to give an 80% chromatographed yield of the cyclopropyl ether N-2. However, treatment of the silyl ether with tetrabutyl ammonium fluoride afforded the enone N-5 rather than the desired ring expanded material N-3. This astonishing result was confirmed by converting compound N-5 into the alpha methyl ketone N-6 (by hydrogenation or dissolving metal reduction), a compound available in two steps from ketone I-6. The enolate of ketone I-6 was alkylated with one equivalent of methyl iodide, and the ketone mixture N-7 was equilibrated to the more stable isomer N-6 (which was identical to the material from the "ring expansion" route). Efforts to expand the ring using diazomethane gave only recovered starting material probably because of steric hindrance to attack at the carbonyl at C-9.

Chart N

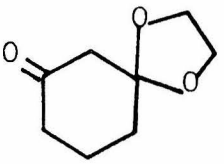

I-6
1) LiN(i-Pr)2
2) t-BuMe2SiCl
95%
OSiMe2t-Bu
N-1
80%
C6H5HgCBrCl2
C6H6, △
1) LiN(i-Pr)2
2) 1 eq. CH3I
100%
t-BuMe2SiO Cl
Cl
N-2
N-7
80%
(n-Bu)4N+F-
THF
(n-Bu)4N+F-
N-5
N-3
KOH
EtOH
99%
H2, Pd/C
or Li, NH3
89%
N-6
N-4



50



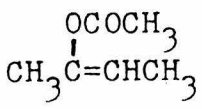
51



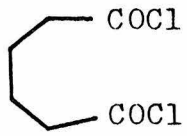
52

Since the ring expansion approach did not look promising, it was decided to utilize homo-Wieland-Miescher ketone (50). Hence, the seven-membered ring would be introduced at the beginning of the synthesis. Compound 50 has in fact been synthesized in two steps by a Robinson annelation between 2-methyl-1,3-cycloheptanedione (51) and methyl vinyl ketone in about 20% to 30% yield (45). However, the synthesis of dione 51 involves a three step ring expansion from compound 52 (itself a relatively expensive compound) with an overall yield of only about 17% (46). Hence, the overall yield of homo-Wieland-Miescher ketone would be only 4%! Clearly, for a multi-step synthesis such as for aphidicolin, a better route to this material was needed.

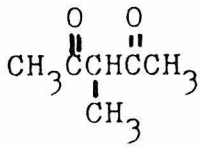
The initial efforts were aimed at finding an efficient high yield synthesis of dione 51. Seven-membered rings are often difficult to form (47). However, there was one report in the literature of a cycloheptanone synthesis via an aluminum trichloride catalyzed cyclization of



53



54

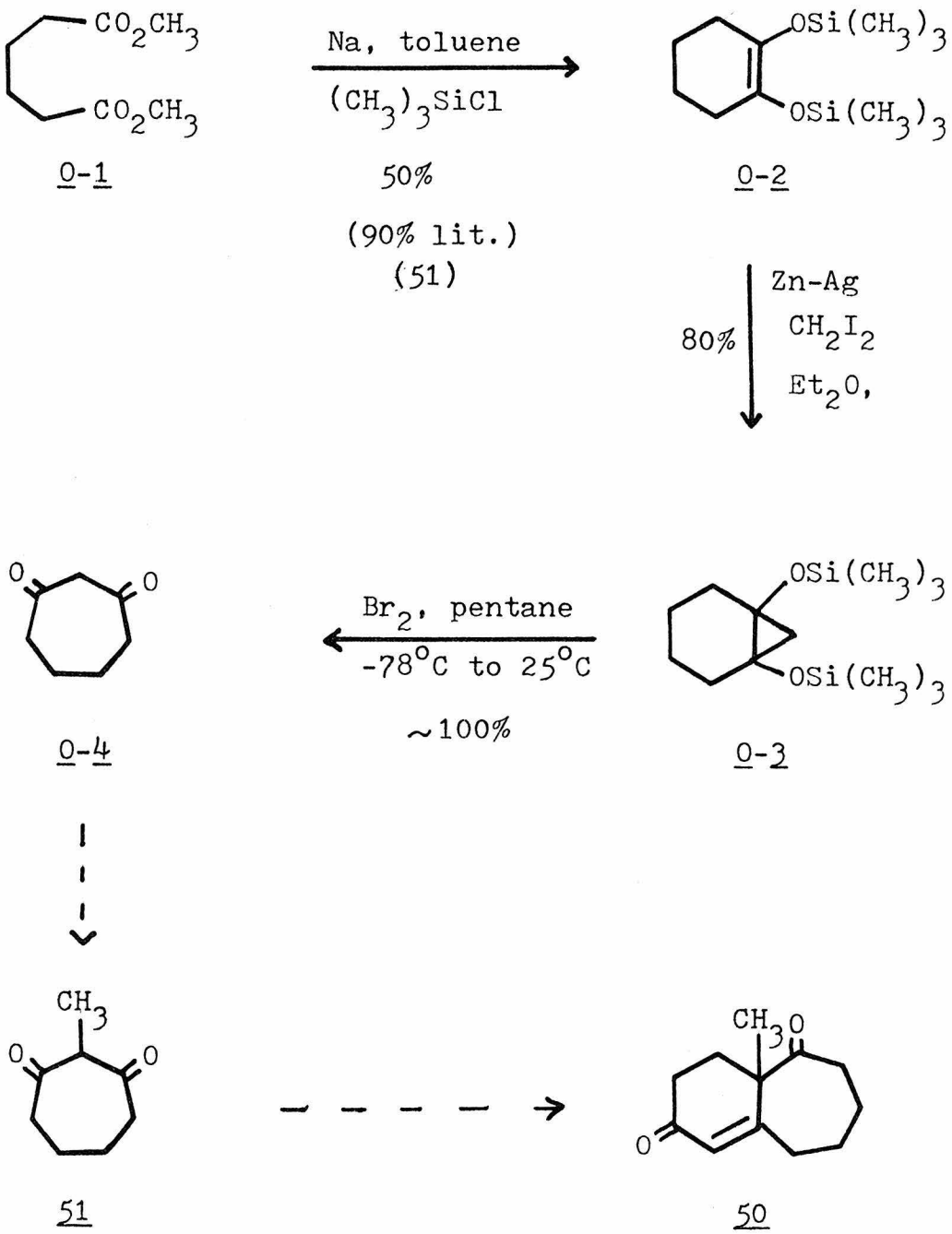


55

6-heptenoyl chloride to give initially a 50% yield of β-chlorocycloheptanone (48). Also, one commercial synthesis of 2-methyl-1,3-cyclopentanedione involves the Lewis acid catalyzed cyclization of succinyl chloride with 2-buten-2-ol acetate (53) (49). When similar reaction conditions were employed with adipoyl chloride (54), the only compound which distilled out of the crude product (a black tar) was methyl acetylacetone (55), a dimerization product of compound 53. Finally, the cyclization using propionic acid rather than the enol acetate of 2-butanone was tried. Despite the fact that this gives a 45% yield of 2-methyl-1,3-cyclopentanedione when reacted with succinyl chloride and aluminum trichloride (50), reaction with adipoyl chloride and $AlCl_3$ led to only 11% of any distillable material, indicating that once again the adipoyl chloride probably just polymerized under the reaction conditions.

A feasible approach to dione 51 was finally realized via the novel ring expansion shown in Chart 0. Acyloin condensation on dimethyl adipate (0-1) in the presence of trimethylsilyl chloride gave the cyclohexene 0-2

Chart O



O-1 O-2 O-3 O-4 51 50

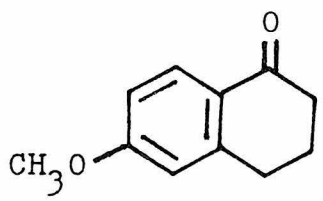
in 50% nonoptomized yield (51). Cyclopropylation (Simmons-Smith reaction) using the method of Conia (52) afforded the cyclopropyl ether O-3 in 80% chromatographed yield. Bromination of O-3 smoothly cleaved the cyclopropane ring and eliminated two moles of $BrSi(CH_3)_3$ to furnish the desired ring expanded material, 1,3-cycloheptanedione (O-4). Conia has used a similar bromination of 1,2-bis-(trimethylsiloxy)cyclobutene to produce 1,2-cyclobutane-dione (53). About a year after the work in Chart O was completed, Saegusa reported virtually the same sequence for ring expansion (54). The main difference between the two approaches is that Saegusa used $Fe^{III}Cl_3$ in the cyclopropane cleavage step to give a 68% yield of 1,3-cycloheptanedione.

Although a convenient, high yield synthesis of 1,3-cycloheptanedione was now available, there were still a number of problems with this route. First, the dione O-4 was a very unstable compound which began to decompose immediately on exposure to air. Also, the alkylation of the cycloheptanedione O-4 to give the dione 51 goes in only 40% to 45% yield (45). More importantly, the yield of homo-Wieland-Miescher ketone 50 from the dione 51 is only 20% to 30% (45). Hence, even if a 60% yield of dione O-4 from dimethyl adipate could be realized, the yield of the desired ketone 50 from this dione would

still only be on the order of about 10%. Since these yields were still too low to provide enough starting material for the synthesis of aphidicolin, it was decided, if possible, to purchase the seven-membered ring.

2-Methoxybenzosuberone (P-1), a commercially available, stable, white solid (55), seemed ideally suited to this purpose. Not only does it contain the desired six and seven membered rings to construct homo-Wieland-Miescher ketone, but also it contains oxygen functionality in the correct positions. Although the compound was not cheap, it does already contain eleven of the twenty carbon atoms required in aphidicolin. Also, 2-methoxybenzosuberone and 2-methyl-1,3-cyclohexanedione (G-1), the starting material for Wieland-Miescher ketone, cost about the same (55), so that there was no great financial disadvantage in using the benzosuberone as starting material.

To convert 2-methoxybenzosuberone into homo-Wieland-Miescher ketone, it was necessary to introduce a bridgehead methyl group. In a synthesis of Wieland-Miescher ketone (H-9) from ketone 56, Birch was able to effect



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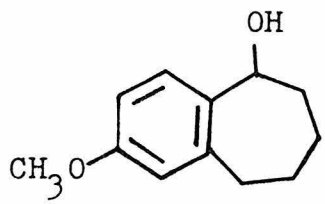
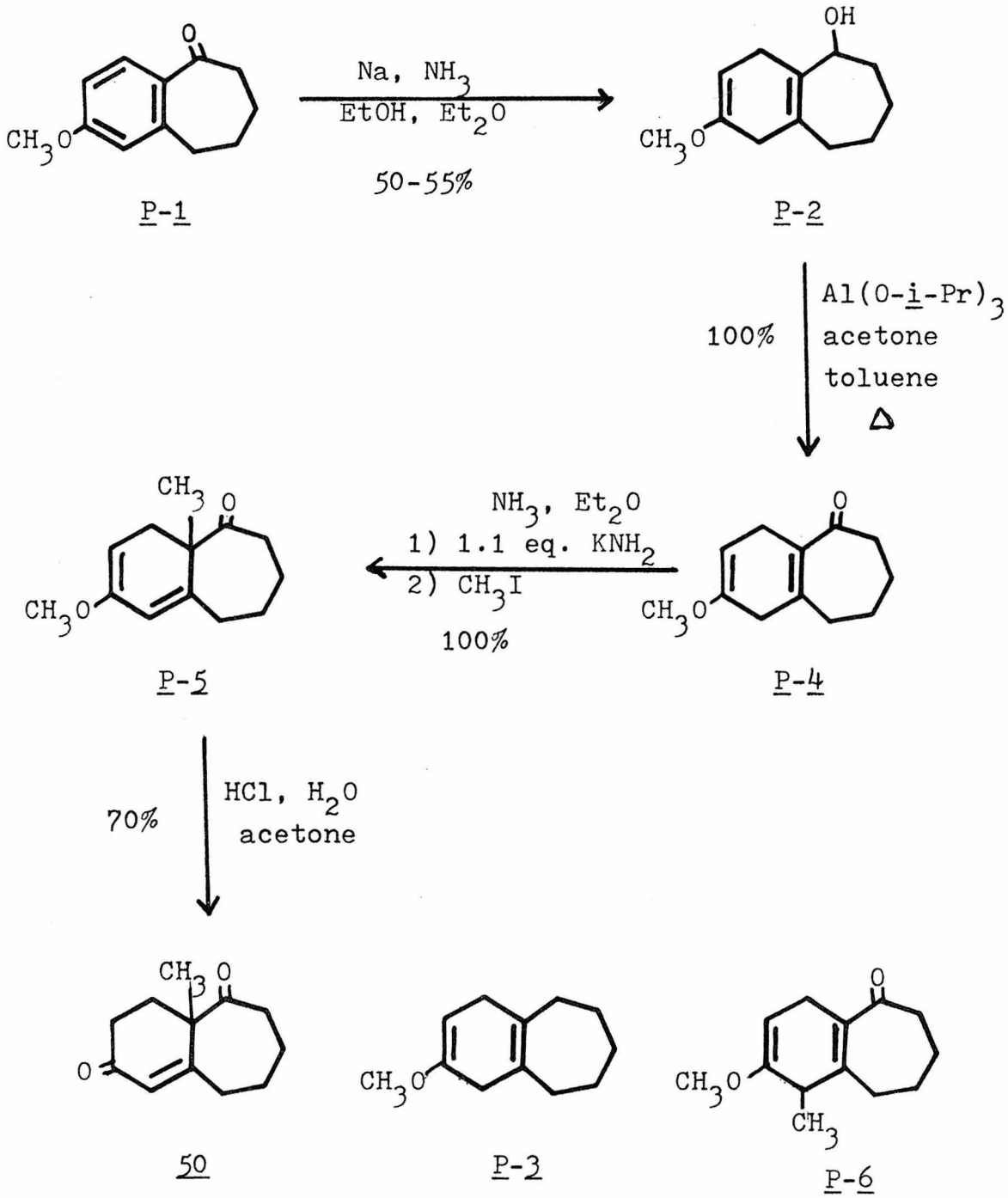


57

such a transformation although in low (20%) overall yield (56). However, this route turned out to work quite well for the synthesis of the seven-membered ring analog (Chart P). Careful reduction of 2-methoxybenzosuberone with sodium in ammonia, ethanol, and diethyl ether afforded about a 50% to 55% yield of alcohol P-2 and about 40% of the overreduction product P-3. In this Birch reduction it was critical that just enough sodium was added to maintain a blue color for 30 minutes. While insufficent sodium or reaction time resulted in the formation of the alcohol 57, excess sodium resulted in greater amounts of the overreduction product P-3 being formed. Although the yield in this step was not that high, it is preferable that the lowest yield steps come early in a long synthesis.

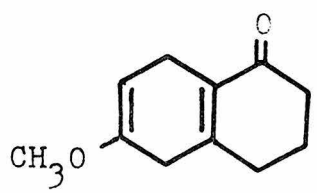
Despite the fact that alcohol P-2 was a readily crystalline and polar white solid, the best way to remove the nonpolar impurity P-3 was by distillation of the low-boiling impurity in a base washed apparatus, leaving the desired compound as the pot residue. All attempts at chromatography of compound P-2 (or compound P-4) always led to substantial olefin isomerization. Likewise, any attempts to distill the high boiling alcohol P-2 or ketone P-4 were not very successful. It was also not feasible to purify the alcohol by crystallization since the resulting crystals were always contaminated by compound P-3.

Chart P

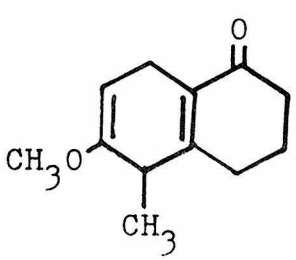

Na, NH3
EtOH, Et2O
50-55%
P-1
P-2
OH
100%
Al(O-i-Pr)3
acetone
toluene
Δ
NH3, Et2O
1) 1.1 eq. KNH2
2) CH3I
100%
P-4
P-5
70%
HCl, H2O
acetone
50
P-3
P-6

An Oppenauer oxidation of alcohol P-2 furnished ketone P-4 in quantitative crude yield. It was necessary to repeat this reaction twice as the first time always resulted in 10% to 20% starting material. Longer reaction times or adding excess aluminum isopropoxide catalyst caused substantial olefin isomerization. Addition of more acetone seemed to have no major effect on the equilibrium.

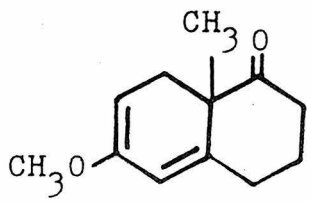
In the work by Birch, alkylation of enone 58 always led to 10% to 15% of the by-product 59 and only 50% to 60% of the desired isomer 60 (56). However, alkylation of ketone P-4 with methyl iodide led exclusively to the methyl ketone P-5 in quantitative crude yield. No evidence was seen for the formation of ketone P-6. This may have something to do with the report that the cycloheptenone double bond readily deconjugates, and compound P-5 may be less strained than compound P-6 (57).



58



59



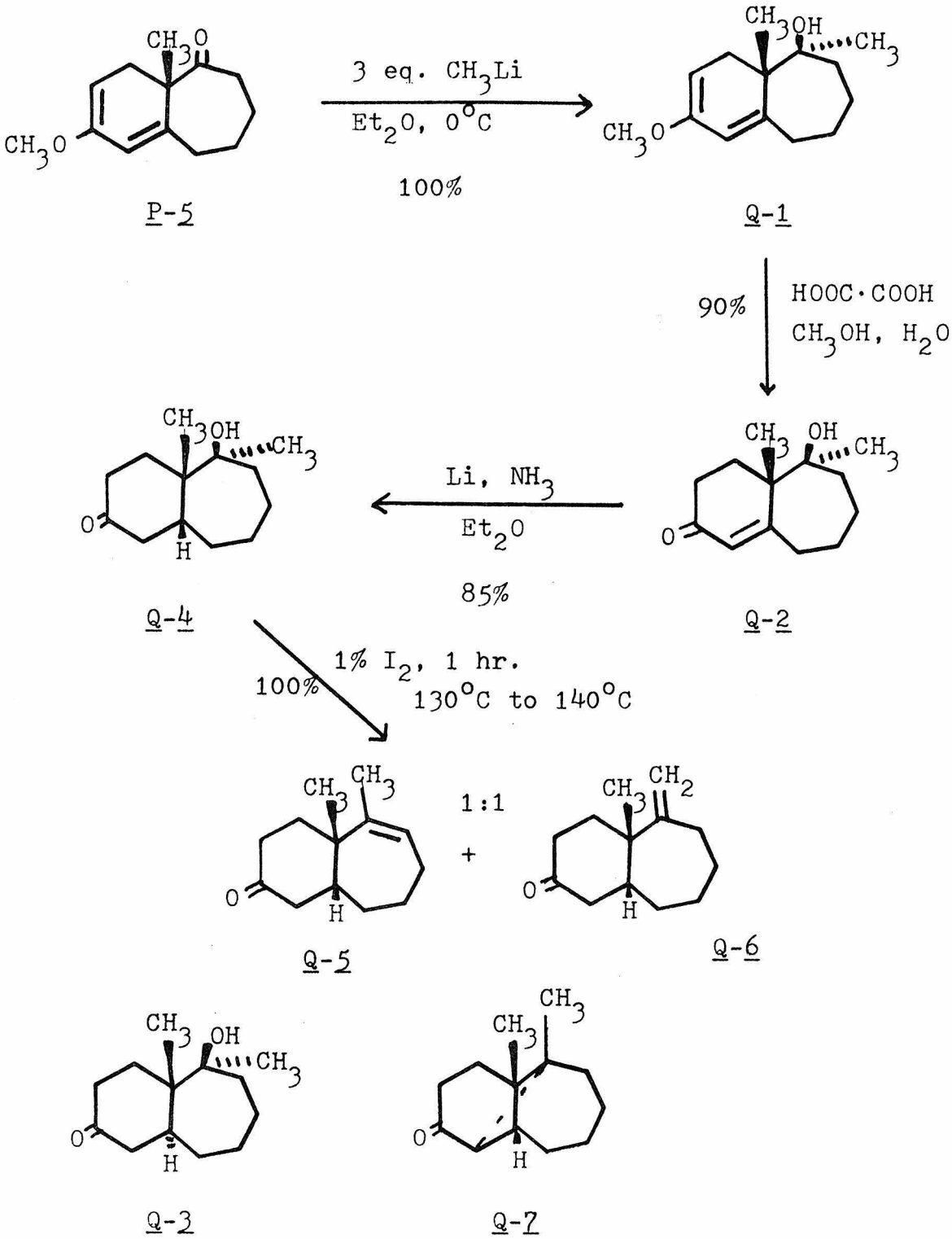
60

Ketone P-5 was readily hydrolyzed to homo-Wieland-Miescher ketone 50 in 70% chromatographed and crystallized yield. The overall yield from 2-methoxybenzosuberone was thus 40%. This represents an improvement in yield over the literature synthesis of compound 50 by a factor of ten (and is also shorter and cheaper) (45).

However, in the synthesis of aphidicolin from 2-methoxybenzosuberone it was actually easier to bypass the homo-Wieland-Miescher ketone since the two ketone functionalities were already distinguished in compound P-5 (one is protected as an enol ether). Hence, ketone P-5 was treated with three equivalents of methyllithium to furnish the tertiary alcohol Q-1 in quantitative crude yield. Although the stereochemistry of this intermediate was not proven, attack from the least hindered side should give the stereochemistry as shown. Use of less than three equivalents of methyllithium in the reaction led to a few per cent of recovered starting material. This indicates that the ketone P-5 is somewhat hindered relative to ketone I-6 (where only slightly over one equivalent of methyllithium was required for the reduction) (35).

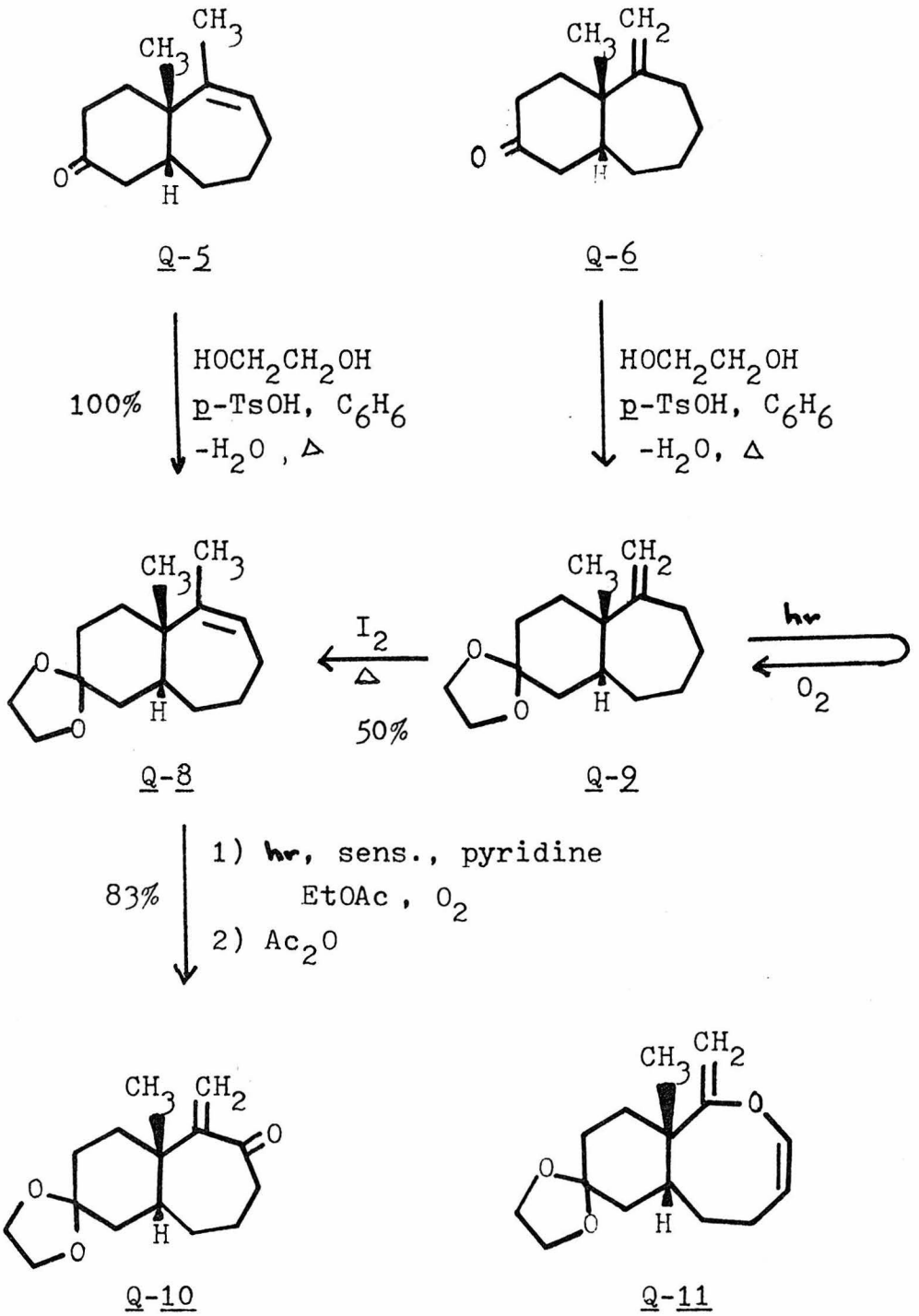
Compound Q-1 was hydrolyzed to the enone Q-2 in about 90% crude yield using oxalic acid. Reduction of the enone Q-2 with lithium in ammonia and diethyl ether (using the tertiary alcohol as proton source) afforded an 85% yield (40% from 2-methoxybenzosuberone)

Chart Q



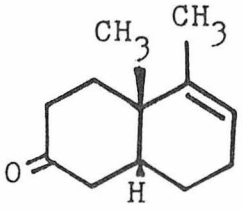
P-5 Q-1 Q-2 Q-4 Q-5 Q-6 Q-3 Q-7

Chart Q (continued)

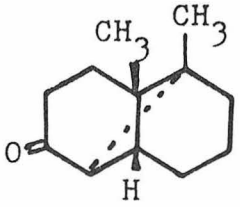


of the cis-fused ketone Q-4 rather than the expected trans-fused ketone Q-3. However, since all literature precedent dictated that the major product should have been trans (58, 59), and only one isomer was produced in the reduction (98% pure by VPC), it was at the time assigned the trans configuration. Not until an X-ray was done on a later intermediate was this unusual result realized.

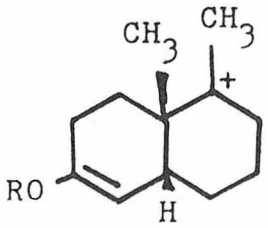
Dehydration of the alcohol Q-4 did not proceed as smoothly as with the six-membered ring analog I-7 (35). Use of thionyl chloride in pyridine led to exclusively the exocyclic olefin Q-6. A one-to-one mixture of the endocyclic and exocyclic olefins Q-5 and Q-6 could be produced by carefully controlled addition of small amounts of iodine to the starting alcohol Q-4 at 130°C to 140°C for one hour under argon. Use of smaller amounts of iodine, lower temperatures, or shorter reaction times gave more of the undesired exocyclic material. On the other hand, use of larger amounts of iodine, higher temperatures, or longer reaction times led to a side product which showed no olefinic protons in the NMR and was probably compound Q-7. Stork showed that compound 62 was produced in 90% yield from olefin 61 via the intramolecular trapping of the carbonium ion 63 by the enol form of the ketone (60). A similar reaction could take place in the seven-membered ring series, and the



61



62



63

formation of the side product Q-7 created the first suspicions that the ring junction was in fact cis and not trans as initially proposed.

The olefins Q-5 and Q-6 could be separated by chromatography but not without substantial loss of material on the column. To completely separate the olefins required a large amount of silica gel and resulted in a yield of about 20% of the desired endocyclic olefin and about 30% of exocyclic olefin. The exocyclic olefin could be converted back into the one-to-one mixture of exocyclic and endocyclic olefins by using iodine exactly as in the dehydration of alcohol Q-4. The ketal Q-8 could be prepared in high yield from the ketone Q-5. Likewise, the ketal Q-9 could be made from the corresponding ketone Q-6. However, an attempt to equilibrate the exocyclic olefin to the endocyclic olefin using a rhodium catalyst (61) gave only recovered starting material, indicating that the olefin was sterically hindered.

Since the exocyclic ketone Q-6 could be prepared in such high yield, it was decided to try to introduce the desired oxygen functionality directly on the ketal Q-9 using selenium dioxide (a Riley oxidation) (62). However, once again there was no reaction at the site of the exocyclic olefin. These results indicated that there was a good chance that the exocyclic olefin would also not react under the conditions of the photooxygenation. Other workers have in fact found out that exocyclic olefins in six membered rings are slow to react because there is no in-plane easily accessible hydrogen atom which can be extracted (63). This indeed turned out to be the case. The olefin Q-9 was completely inert under all photooxygenation conditions employed. On the other hand, pure olefin Q-8 was readily converted to the desired methylene ketone Q-10 in chromatographed yield of 83%. This high yield in the photooxygenation (also called the Schenck reaction) was probably because the formation of the strained by-product Q-11 (analogous to I-9 in Chart I) required attack by oxygen at the sterically hindered position (C-10) alpha to the bridgehead methyl. In the six-member ring case the photooxygenation furnished only a 55% yield of the methyl ketone H-8 (and a 35% yield of the by-product I-9) (35). However, in the photooxygenation of Q-8, no by-product was ever observed.

Hence, the route finally taken was to ketalize the one-to-one mixture of endocyclic and exocyclic olefins Q-5 and Q-6 (85% distilled yield), and then perform the photooxygenation on the ketal mixture (Q-8 and Q-9). A simple column filtration on Florisil was all that was necessary to separate the nonpolar, fast eluting, unreacted exocyclic olefin from the polar methylene ketone Q-10. Heating the exocyclic olefin Q-9 with iodine led once again to about a one-to-one olefin mixture, and this mixture could then be subjected to the photooxygenation. No major loss of material was observed by this type of recycling because the exocyclic olefin was never very long on the column during chromatography.

With an effective route to methylene ketone Q-10 available (in nine steps with an overall yield from 2-methoxybenzosuberone of about 30% based on recovered exocyclic olefin Q-9), attention was turned to the synthesis of the spiro ketone R-7 (Chart R). A Diels-Alder reaction of Q-10 with methyl methacrylate for twenty-four hours in a base washed sealed tube at 170°C afforded an 80% chromatographed yield of esters R-1 and R-2 in about equal amounts. However, if the Diels-Alder reaction was run at 220°C, the ratio of R-2 (the ester for the stemodin series) to R-1 was about two-to-one. On the other hand, when the reaction was performed at 160°C, this ratio was reversed; i.e., the ratio of the ester for the aphidicolin

Chart R

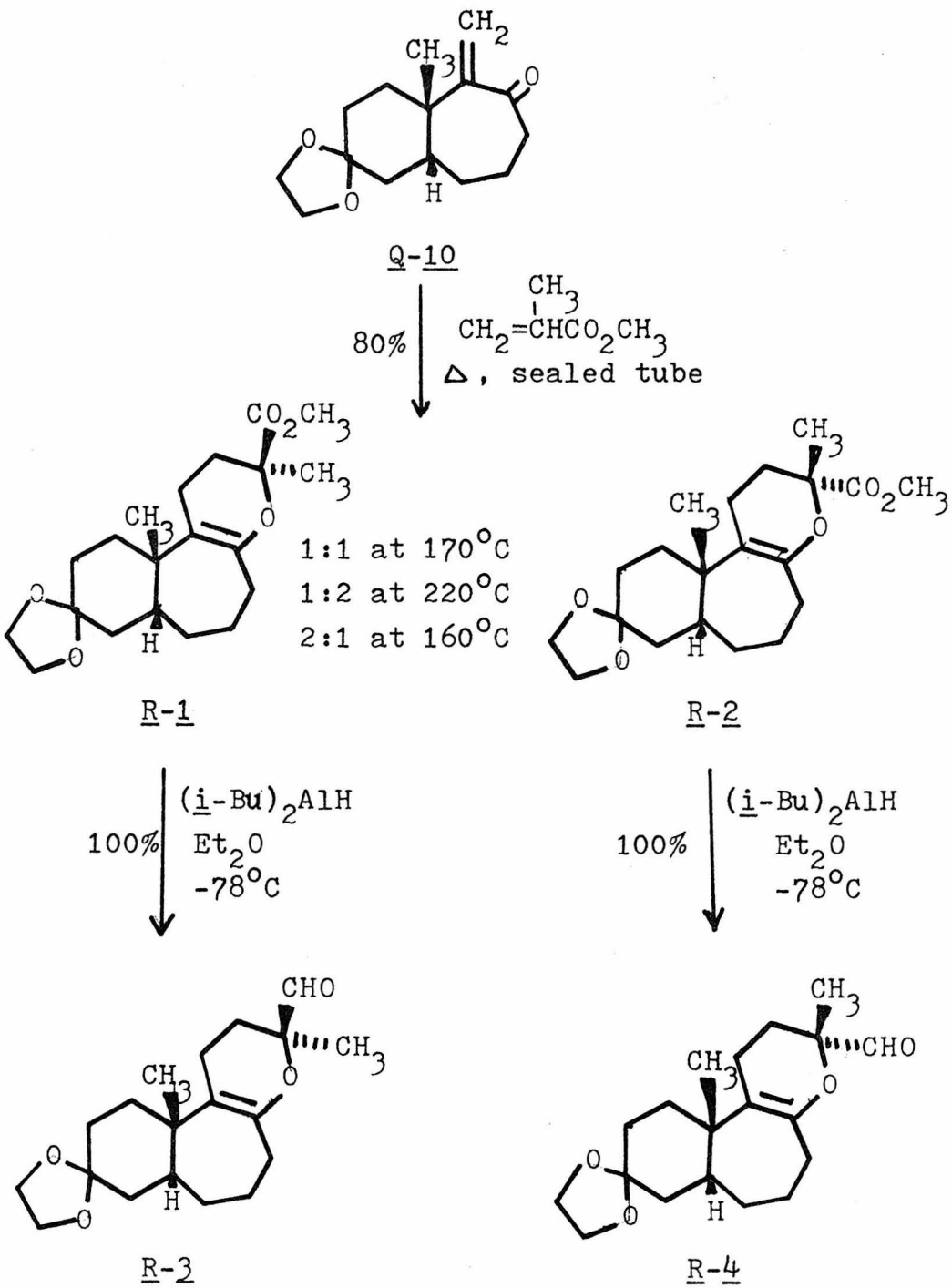
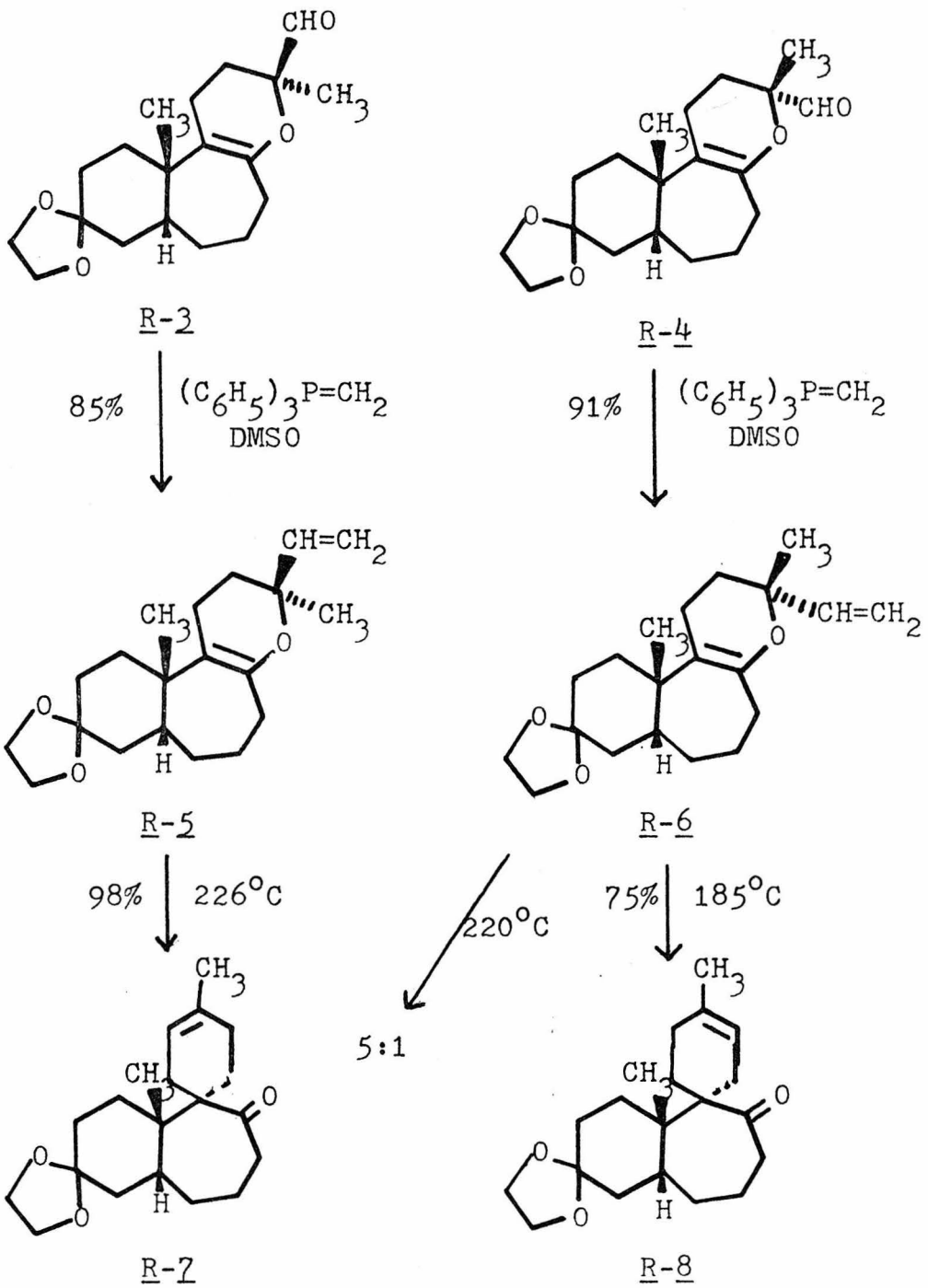

CH2
CH3
O
O
O
H
Q-10
80%
CH3
CH2=CHCO2CH3
Δ, sealed tube
CO2CH3
CH3
CH3
O
O
O
H
1:1 at 170°C
1:2 at 220°C
2:1 at 160°C
R-1
CH3
CH3
CO2CH3
O
O
O
H
R-2
100%
(i-Bu)2AlH
Et2O
-78°C
100%
(i-Bu)2AlH
Et2O
-78°C
CHO
CH3
CH3
O
O
O
H
R-3
CH3
CH3
CHO
O
O
O
H
R-4

Chart R (continued)



series (R-1) to R-2 was about two-to-one. Hence, by varying the temperature, the Diels-Alder could be induced to give a predominance of either isomer so that either the aphidicolin or stemodin series could be entered preferentially.

Esters R-1 and R-2 could be separated by medium pressure liquid chromatography, and reduced to the corresponding aldehydes R-3 and R-4 in quantitative crude yield with three equivalents of diisobutylaluminum hydride at -78°C in diethyl ether. A Wittig reaction was then performed on the aldehydes to give olefins R-5 and R-6 in respectively 85% and 91% crystallized and chromatographed yields.

Whereas the six-membered ring analog 36 of olefin R-6 rearranges smoothly at 170°C (Chart J), heating olefin R-6 (stemodin series) for one hour at 170°C gave a two-to-one mixture of spiro ketone R-8 to starting material. However, heating olefin R-6 for one hour at 185°C afforded less than 10% starting material. Similarly, olefin R-5 (aphidicolin series) had to be heated at a higher temperature than the corresponding six-membered ring analog H-7 to effect complete transformation. Heating olefin R-5 for one hour at 226°C gave a nearly quantitative yield of the desired spiro ketone R-7. Surprisingly, the Claisen rearrangement of olefin R-6 at 220°C for one hour afforded about a five-to-one ratio

of spiro ketones R-7 to R-8. Since heating a pure sample of spiro ketone R-8 at 230°C for one hour gave only recovered starting material, the rearrangement of olefin R-6 at 220°C was probably a radical, nonconcerted process.

This was a fortuitous result since it meant that not only was the aphidicolin isomer the major product in the Diels-Alder reaction (when run at 160°C), but also the Claisen rearrangement of the olefin in the stemodin series furnished mainly the spiro ketone for the aphidicolin synthesis. It also meant that it was not necessary to separate the two esters R-1 and R-2 from the Diels-Alder reaction. The isomer mixture was in fact converted directly into the aldehyde mixture R-3 and R-4, and a Wittig reaction on this mixture gave the olefin mixture R-5 and R-6. A thermal Claisen at about 220°C gave mainly the desired spiro ketone R-7. Ketone R-7 was readily crystalline and could be fractionally crystallized from the Claisen mixture to give overall a 50% yield from the ester mixture. Additional material (though of lower purity) could be obtained by column chromatography of the Claisen mixture of ketones to give a 59% yield of material which was 90% pure by VPC. Hence, the spiro ketone R-7 was available in thirteen steps from 2-methoxybenzosuberone with an overall yield of about ten per cent (about 84% per step), and no difficult chromatographies were really required.

The initial assignment of stereochemistry to esters R-1 and R-2 was based on similar arguments as the stereochemical assignments of esters J-1 and J-2. For example, pseudoaxial ester R-1 was faster eluting than ester R-2. More importantly, because of steric hindrance from the bridgehead methyl group, the Claisen for olefin R-5 required a much higher temperature than that for olefin R-6. More conclusive evidence came from comparison of the carbon-13 NMR spectra of the two spiro ketones R-7 and R-8. Because of a phenomenon known as the steric compression shift, carbon atoms which are sterically crowded appear at higher field (lower ppm) than those less crowded (64). Comparison of the shifts of the olefinic carbon substituted with hydrogen in the spiro ring in ketones R-7 and R-8 showed an upfield shift of 2.5 ppm in R-7. This is because the olefin carbon in R-7 is close to the bridgehead methyl. Finally, this assignment was confirmed by an X-ray of spiro ketone R-7 by Professor Jon Bordner of North Carolina State University.

Now, attention was turned towards the ring contraction (Chart S). However, spiro ketone R-7 turned out to be even more hindered than the six-membered ring analog H-6. Using the standard conditions (refluxing with potassium t-butoxide in t-butanol containing isoamyl nitrite) to make the oximo ketone S-1 gave only starting material R-7. Evidently, the conditions were not basic enough to

Chart S

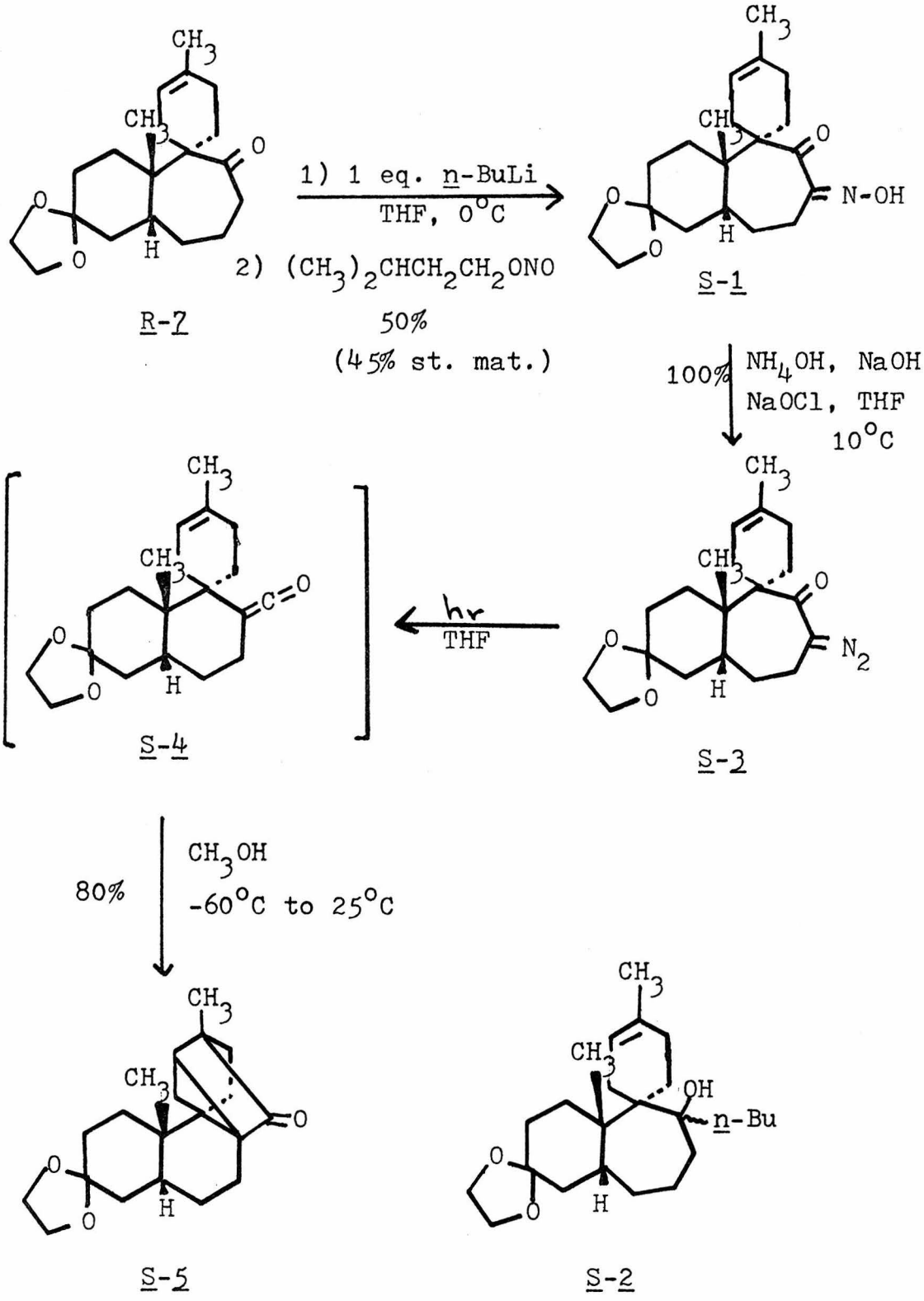
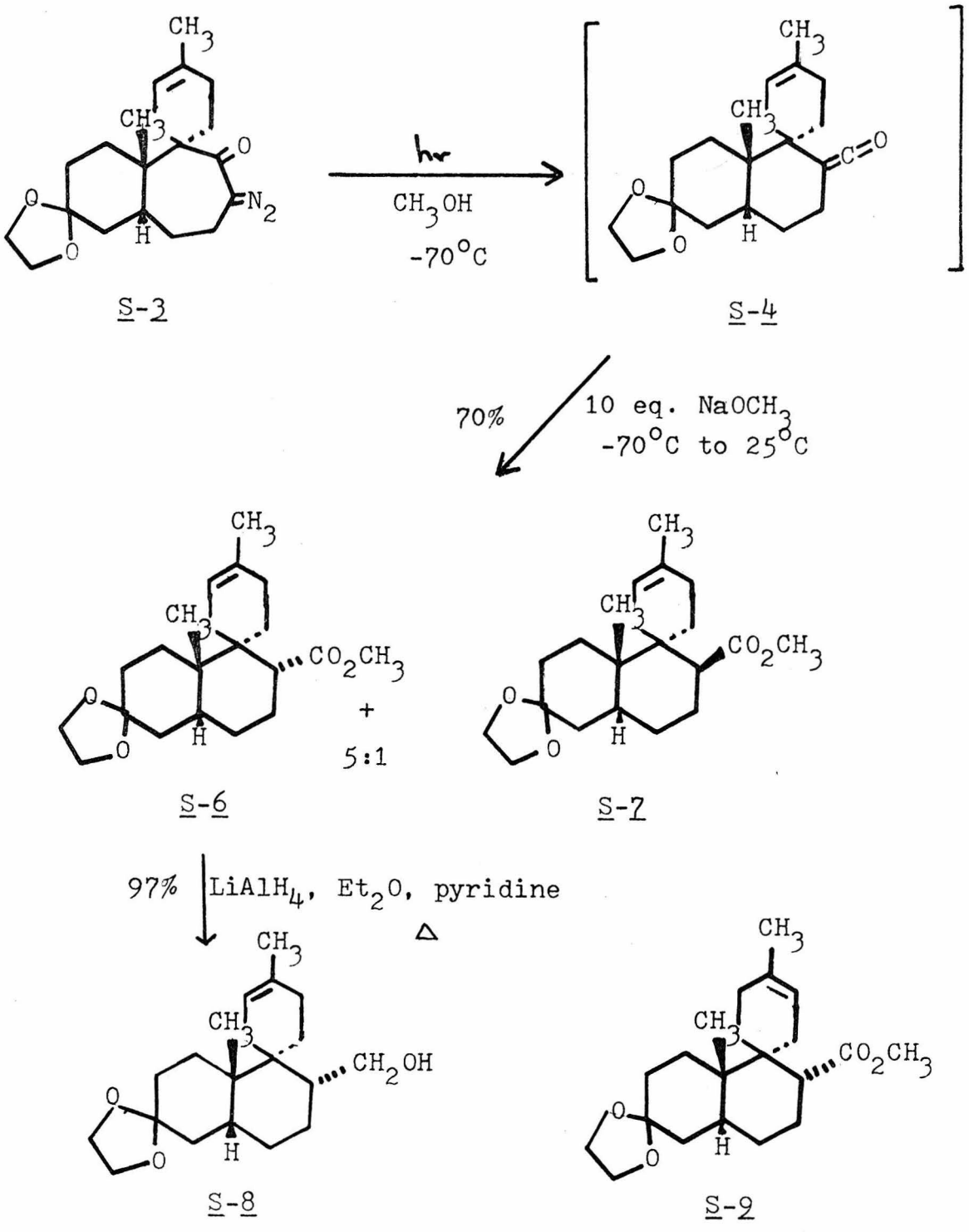

CH3
CH3
O
O
O
H
R-7
1) 1 eq. n-BuLi
THF, 0°C
2) (CH3)2CHCH2CH2ONO
50%
(45% st. mat.)
CH3
CH3
O
N-OH
O
O
H
S-1
100%
NH4OH, NaOH
NaOCl, THF
10°C
CH3
CH3
O
N2
O
O
H
S-3
hr
THF
CH3
CH3
C=O
O
O
H
S-4
80%
CH3OH
-60°C to 25°C
CH3
CH3
O
O
O
H
S-5
CH3
CH3
OH
n-Bu
O
O
H
S-2

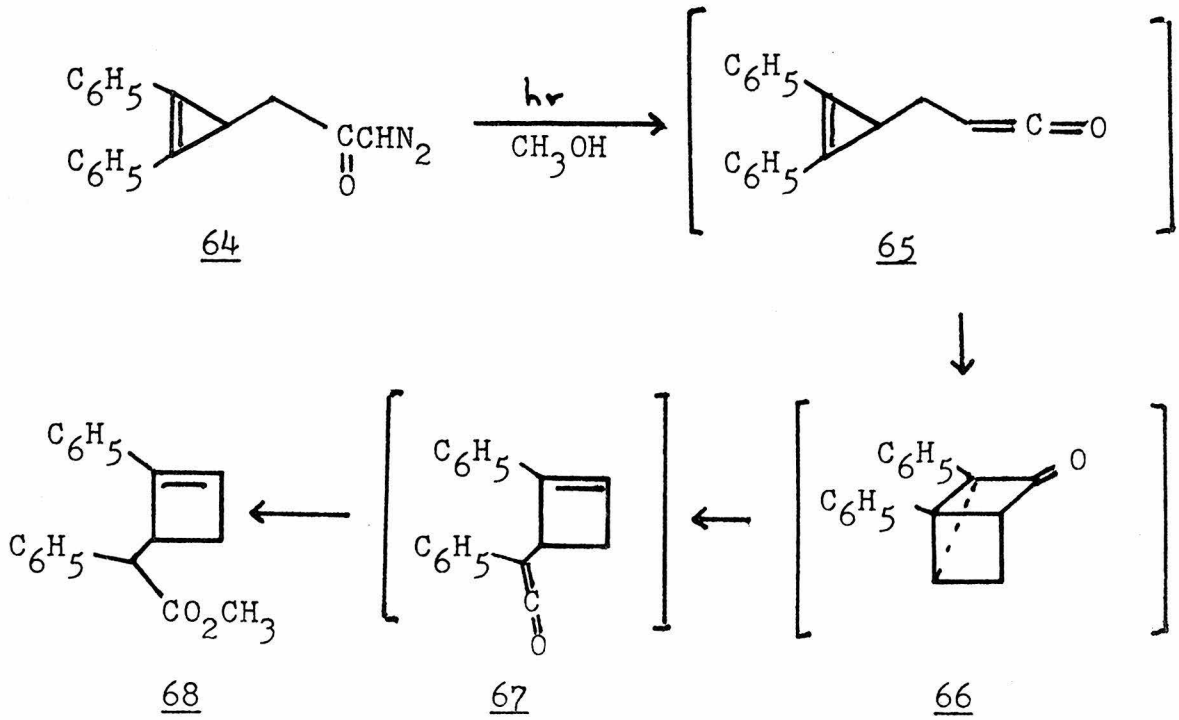
Chart S (continued)



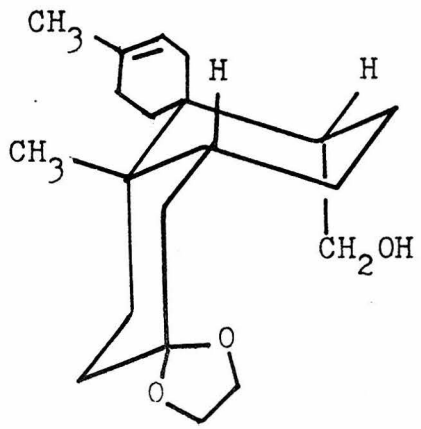
enolize the ketone. The best conditions found to effect the reaction were to enolize the ketone with one (or slightly less than one) equivalent of n-butyllithium in tetrahydrofuran at 0°C and then add one equivalent of isoamyl nitrite. Since the spiro ketone R-7 was so hindered, there was no appreciable amount of tertiary alcohol S-2 produced. However, since the oximo ketone S-1 that was formed was much more acidic than the starting material, proton transfer rapidly took place and only a 50% yield of S-1 was possible from this reaction (along with about 45% starting material). Separation of the product and starting material was trivial because the oximo ketone was a polar solid and was practically insoluble in ether. Hence, it was easy to recycle the starting spiro ketone with the loss of less than 10% of material.

Conversion of the oximo ketone into the diazo ketone was accomplished in high yield using chloramine (the Forster reaction). However, photolysis of the crude diazo ketone S-3 using the identical conditions (one hour in methanol at room temperature) for ring contraction of M-2, the six-membered ring analog, gave a single compound with no olefinic protons in the NMR and a cyclobutanone in the IR. Inspection of molecular models indicated that the intermediate ketene S-4 was perfectly oriented to undergo a thermal concerted $[\pi^2_s + \pi^2_a]$ cycloaddition to produce the unusual tricyclo $[4.2.0.0^{4,7}]$ octane

ring system in S-5. Since this by-product resulted probably from a thermal reaction, the photolysis was tried at about -60°C in methanol for one hour before warming to room temperature. However, the only product isolated from the Wolff rearrangement was once again the cyclobutanone S-5 with no evidence for any ester formation. Evidently, the ketene was stable at -60 °C in methanol, and by the time it had reached a temperature where it would be trapped by methanol, it had already undergone the [2+2] cycloaddition, a favored process since it was intramolecular. Masamune has shown that such an intramolecular addition takes place during the photolysis of diazo ketone 64 (65).



The problem was finally solved by performing the photolysis at low temperature in methanol containing ten equivalents of sodium methoxide. If there had been a proton alpha to the ketone, side reactions could have taken place (66); however, it appeared that the only reaction path available to diazo ketone S-3 was through the ketene S-4 which could then be trapped by the more nucleophilic methoxide (67). This was indeed the case, and as long as the temperature during the Wolff rearrangement was kept below -70°C, none of the cyclobutanone was produced. Instead, about a six-to-one ratio of esters was produced. The esters were easily separated by column chromatography to give about 11% yield of ester S-7 and 59% yield of ester S-6. The structure of the desired ester S-6 was confirmed by an X-ray done of the alcohol S-8 (by Professor Jon Bordner at North Carolina State University). The X-ray showed that in the crystal the preferred orientation of the cis-fused ring was with the bridgehead methyl equatorial so that the hydroxymethyl was axial (compound 69). Attempts to equilibrate



69

either ester with refluxing sodium methoxide in methanol simply gave recovered starting material. Evidently, proton abstraction was once again difficult because of steric hindrance. When lithium diisopropylamide was used to generate the enolate of ester S-7, and the solution warmed to -10°C before quenching with water, a mixture of starting material and cyclobutanone S-5 was produced, indicating that the ester enolate had probably eliminated methoxide to give the ketene S-4.

However, the X-ray of alcohol S-8 showed substantial contamination by the isomer T-1 from the stemodin series (Chart T). By NMR, TLC, and VPC both the alcohol S-8 and the starting ester S-6 appeared to be pure. However, a carbon-13 NMR of ester S-6 showed that about 20% to 25% of the ester S-9 was present. Moreover, when the ester S-6 was reduced by lithium aluminum hydride in refluxing ether, the resulting alcohol S-8 was now only about 67% pure, and another 5% to 10% of the stemodin isomer T-1 had been formed. It was not possible to purify either the ester S-6 or the alcohol S-8 by crystallization or chromatography. The mechanism of the formation of the stemodin series isomer is not clear. It may have something to do with the proximity of ester, alcohol, or ketone group to the olefin in the spiro ring. Any Lewis acid coordinating to these groups may have been transferred intramolecularly to the double bond in the spiro ring. Since the starting spiro ketone R-7

Chart T

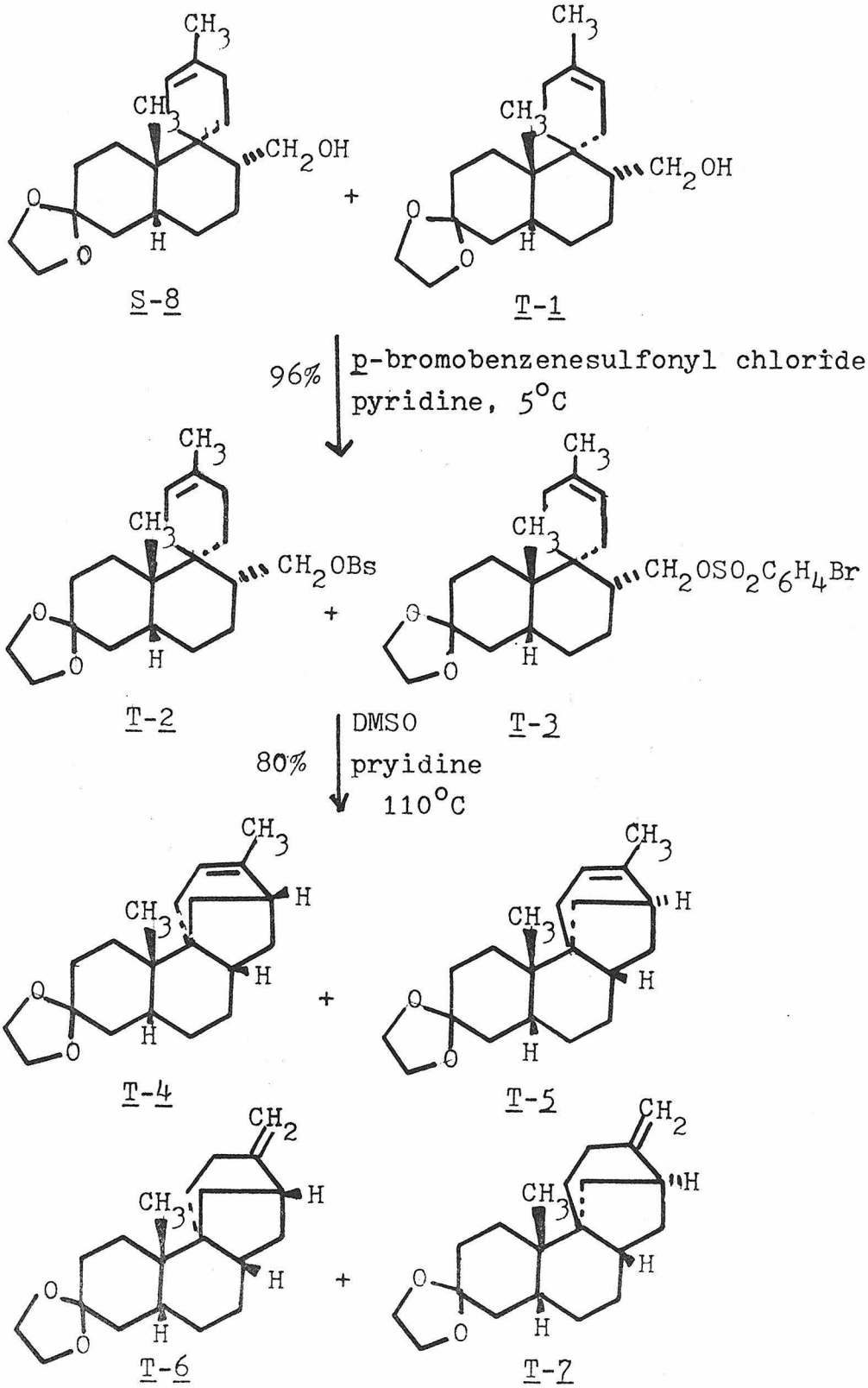
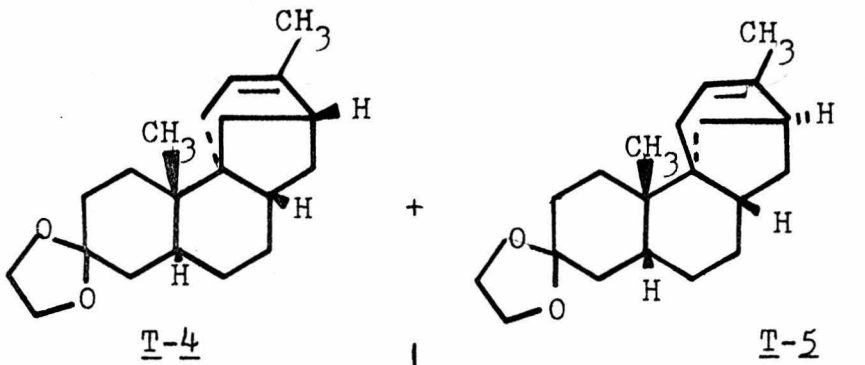
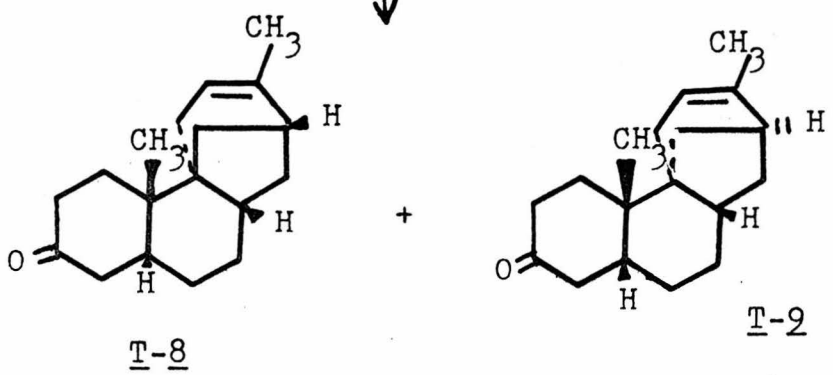

CH3
CH3
CH2OH
O
O
H
S-8
+
T-1
96%
p-bromobenzenesulfonyl chloride
pyridine, 5°C
CH2OBs
T-2
CH2OSO2C6H4Br
T-3
DMSO
80%
pryidine
110°C
T-4
T-5
CH2
T-6
T-7

Chart T (continued)

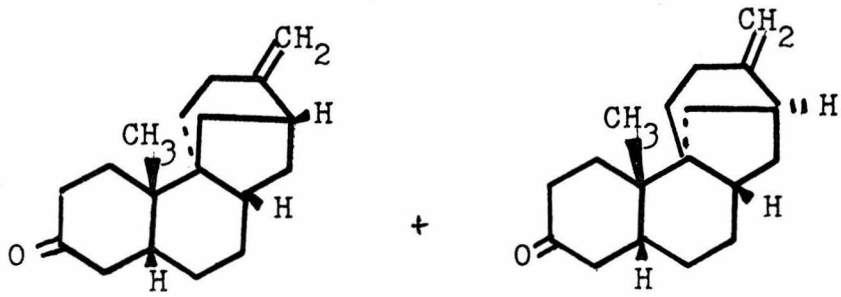


T-4 + T-5

82% HOOC·COOH, CH_3OH, H_2O



T-8 + T-9



T-10 + T-11

was only 90% pure by VPC, there was an average of about 5% olefin isomerization in each step. In any one step, the equilibration was not serious, but overall it presented a problem in purification which was not solved until later in the synthesis.

The alcohol mixture S-8 and T-1 was treated with p-bromobenzenesulfonyl chloride in pyridine to afford the brosylates T-2 and T-3 in nearly quantitative crude yield. Following the procedure of Fráter (68), the crude brosylate mixture was then heated at 110°C for one hour in dimethyl sulfoxide and pyridine to give mainly the tetracyclic endo-olefins T-4 and T-5. Less than ten to twenty percent of the exocyclic olefins (T-6 and T-7) were produced in the solvolysis. Hydrolysis of the ketal with oxalic acid led to about a one-to-one ratio of endocyclic olefins T-8 and T-9 in about 70% overall chromatographed yield from the ester mixture S-6 and S-9. In a separate experiment, 90% pure ester S-6 gave 84% pure alcohol S-8 which was converted into 75% pure endocyclic olefin T-4.

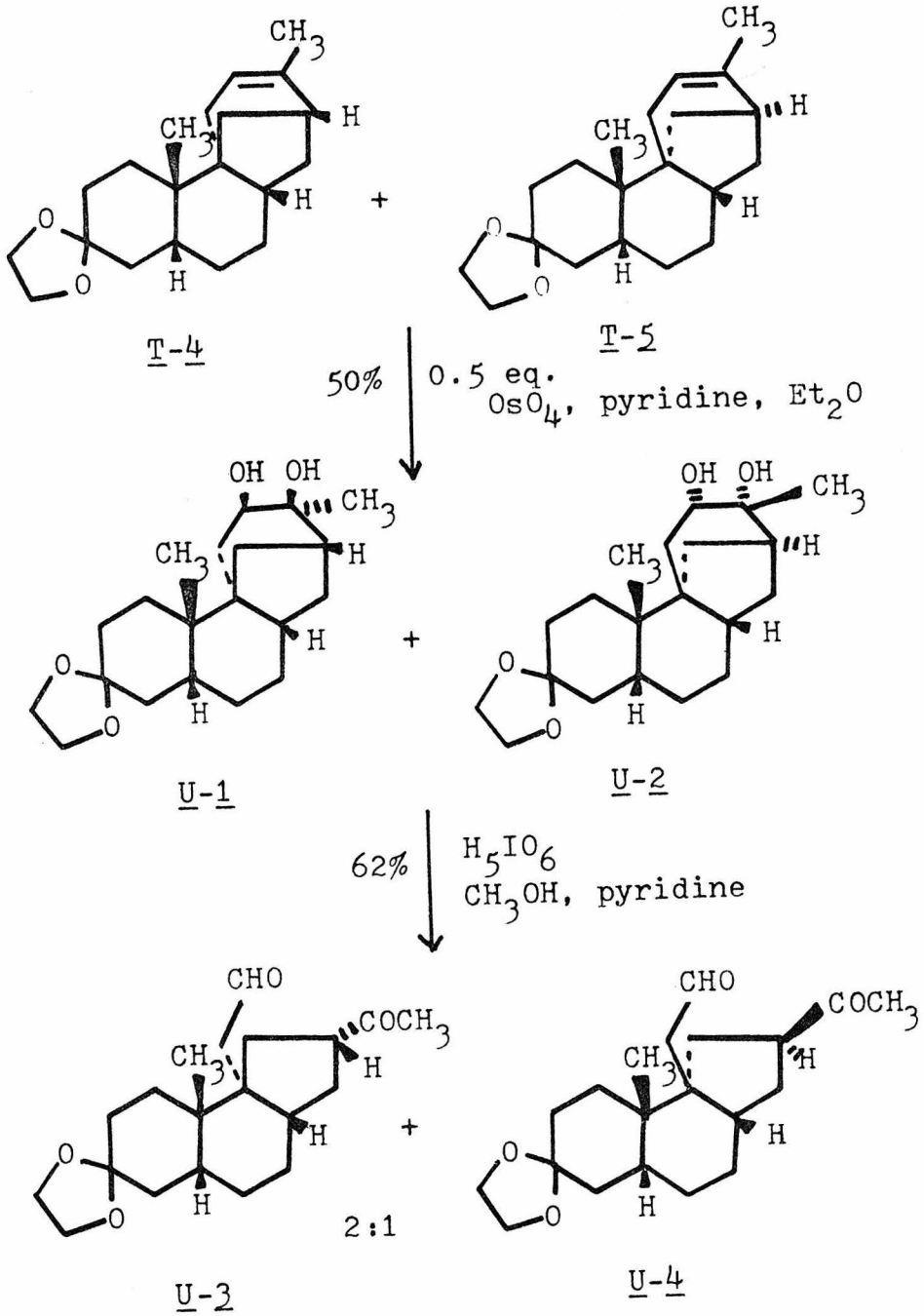
Only at the spiro ketone stage (R-7 and R-8) and after the solvolysis of the brosylates T-2 and T-3 was it possible to clearly distinguish the aphidicolin series from the stemodin series by either NMR or VPC. However, it was still not feasible to separate the olefins T-8 and T-9 by chromatography on silica gel. Also the solvolysis gave mainly the endocyclic olefins. No conditions could be

found to form mainly the exocyclic compounds. Efforts to photochemically isomerize the endocyclic olefins (T-4 and T-5) to the exocyclic olefins (T-6 and T-7) using the method of Marshall (69) were totally unsuccessful. Actually, this was not surprising since rigid systems which cannot accommodate a twisted olefin triplet (or possibly a transitory trans olefin) do not undergo such an isomerization (70). Hence, although the efficacy of the intramolecular solvolysis had been demonstrated, there were still some problems to be solved.

To make certain that the endocyclic olefins T-4 and T-5 were the major products from the solvolysis in pyridine and dimethyl sulfoxide some degradative work was undertaken (Chart U). Hydroxylation of the olefin mixture T-4 and T-5 with one-half an equivalent of osmium tetroxide (71) afforded 51% chromatographed yield of the diol mixture U-1 and U-2 and 47% yield of starting material. There was no selectivity as far as for which olefin isomer was osmylated; however, since it appeared only two new products were formed, it was assumed that osmylation took place from the least hindered side to give the stereochemistry as shown in U-1 and U-2. The diol mixture was then oxidatively cleaved by periodic acid (the Malaprade reaction) to give, after chromatography on silica gel, the keto aldehyde U-3 (eluted first) and U-4.

Before the results of the first X-ray had arrived, and

Chart U


CH3
CH3
H
H
H
O
O
+
T-4
T-5
50%
0.5 eq.
OsO4, pyridine, Et2O
OH OH
CH3
U-1
U-2
62%
H5IO6
CH3OH, pyridine
CHO
COCH3
2:1
U-3
U-4

it was believed that the A/B ring fusion was trans, an attempt was made to introduce the remainder of the A-ring functionality. Since in a trans-fused system a ketone at the three position (steroid numbering) will enolize (kinetically and thermodynamically) towards the two position, it was necessary to protect the two position by the introduction of the double bond as shown in Chart V. Hence, the ketone mixture T-8 and T-9 was converted to the 2-hydroxymethylene mixture V-1 and V-2 in high yield. The double bond was introduced by stirring with 1.2 equivalents of DDQ (2,3-dichloro-5,6-dicyano-1,4-benzoquinone) in dioxane for three minutes at room temperature (72). The aldehyde groups in V-3 and V-4 were removed by refluxing in benzene with one equivalent of tris-(triphenylphosphine)chlororhodium. The overall chromatographed yield of enones V-5 and V-6 from starting ketones T-8 and T-9 was 54%. Alkylation with methyl iodide afforded a quantitative yield of the alpha methyl ketones V-7 and V-8. However, all attempts to introduce a hydroxymethyl at the four position were unsuccessful. Efforts to trap the enolate of V-7 and V-8 with formaldehyde at -78°C using Stork's procedure (73) or with ethyl formate (to give a β-keto aldehyde) gave only recovered starting material, probably because of steric hindrance at the four position and also because both of these reactions were reversible.

Chart V

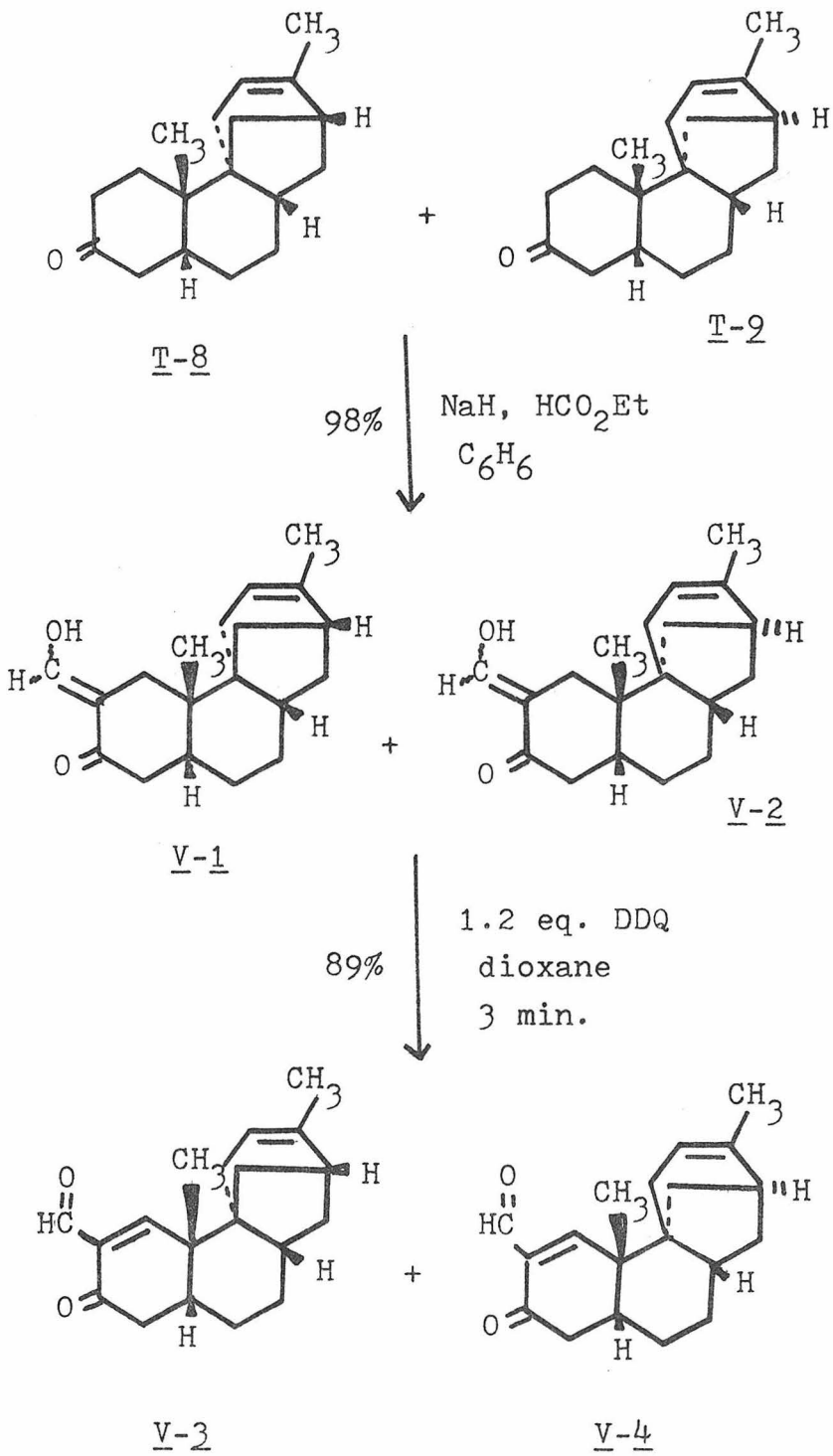
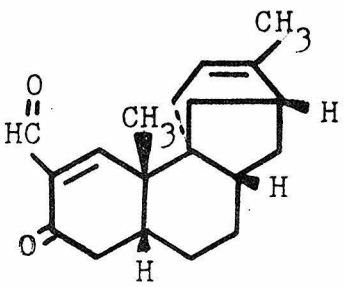
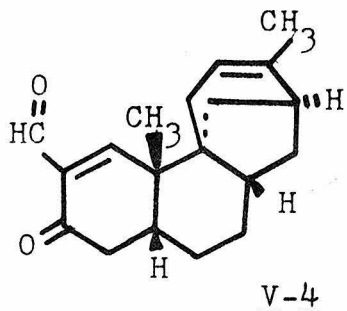

CH3
CH3
H
H
O
H
+
T-8
T-9
98%
NaH, HCO2Et
C6H6
OH
H
C
V-1
V-2
89%
1.2 eq. DDQ
dioxane
3 min.
HC
V-3
V-4

Chart V (continued)

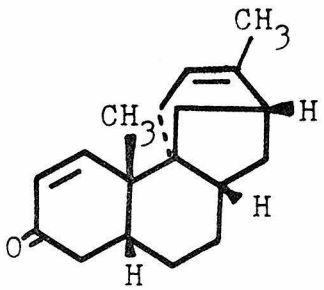


V-3

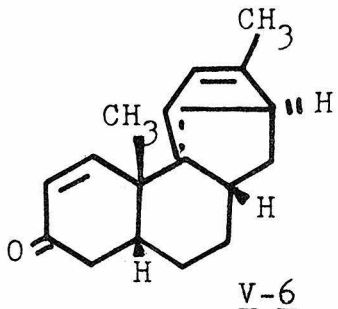


V-4

62% $(C_6H_5)_3RhCl$, C_6H_5, Δ

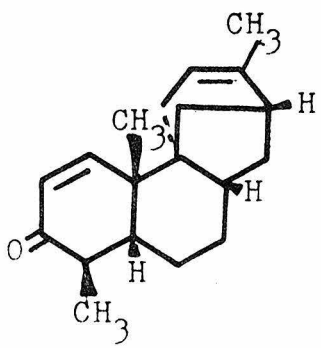


V-5

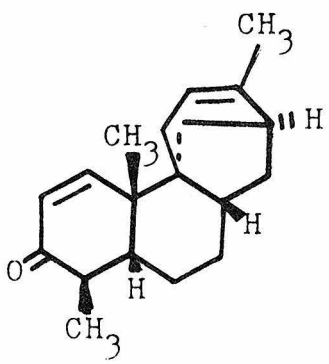


V-6

100% 1) $LiN(\underline{i}\text{-}Pr)_2$, THF, -78°
2) CH_3I



V-7

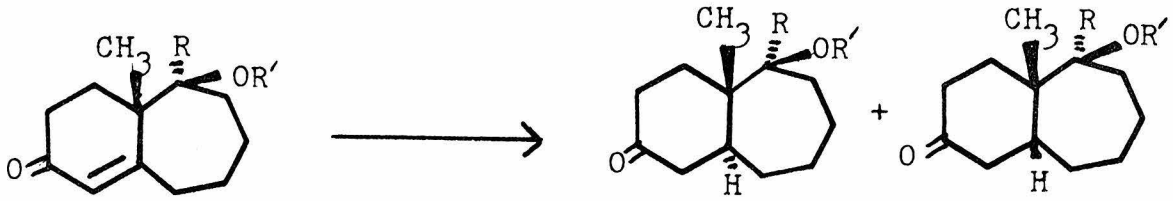


V-8

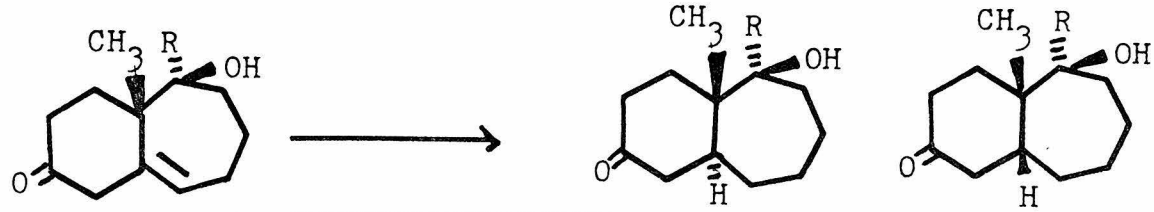
When the results of the first X-ray arrived indicating a cis A/B ring fusion, it was necessary to go back and study the reduction of enone Q-2 (Chart W) to find out what the problem was. At first it was thought that this unusual result was due to steric hindrance by the alpha methyl group at C-10 to protonation at C-5 from the alpha face. Hence, enone W-1 was synthesized (Chart X) and subjected to reduction by lithium in ammonia. The result was an increase in the amount of trans-fused material that was formed, so the alpha-methyl at C-10 was part of the problem. However, the ratio of cis- to trans-fused material was still 9:1. One possibility could still have been the intramolecular protonation by the beta alcohol at C-10. Therefore, this alcohol was protected as the tetrahydropyranyl ether W-2. However, lithium in ammonia reduction of W-2 also gave a 9:1 cis to trans ratio. The problem was therefore the bridgehead methyl group since the reduction of compound W-5 with a hydrogen at the bridgehead gives mainly the trans ring fusion as shown in Chart W (58,59). One possibility is that protonation from the alpha face forces the bridgehead methyl into close contact with the beta hydrogen at C-7 and so this mode of reaction is suppressed on steric grounds.

Two similar cases have recently been observed with the hydroindanone systems shown on the next page (74). Reduction of the enone 70 with lithium in ammonia gave a 99:1 ratio of trans-fused ketone 71 to cis-fused ketone 72.

Chart W

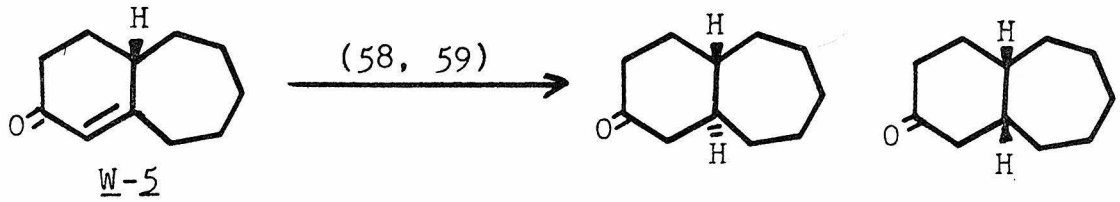


		Trans:Cis	Yield
W-2 : R=H; R′=THP	Li, NH_3, Et_2O 1 eq. t-BuOH	1:9	94%
W-1 : R=R′=H	Li, NH_3, Et_2O	1:9	95%
	HOAc, 1 atm. H_2 10% Pd/C	1:2	90%
	HOAc, 3 atm. H_2 10% Pd/C	1:2	85%
	1% KOH, 10% Pd/C 1 atm. H_2, EtOH	2:3	85%
Q-2 : R=CH_3; R′=H	Li, NH_3, Et_2O	1:49	99%
	HOAc, 1 atm. H_2 10% Pd/C	0:100	100%



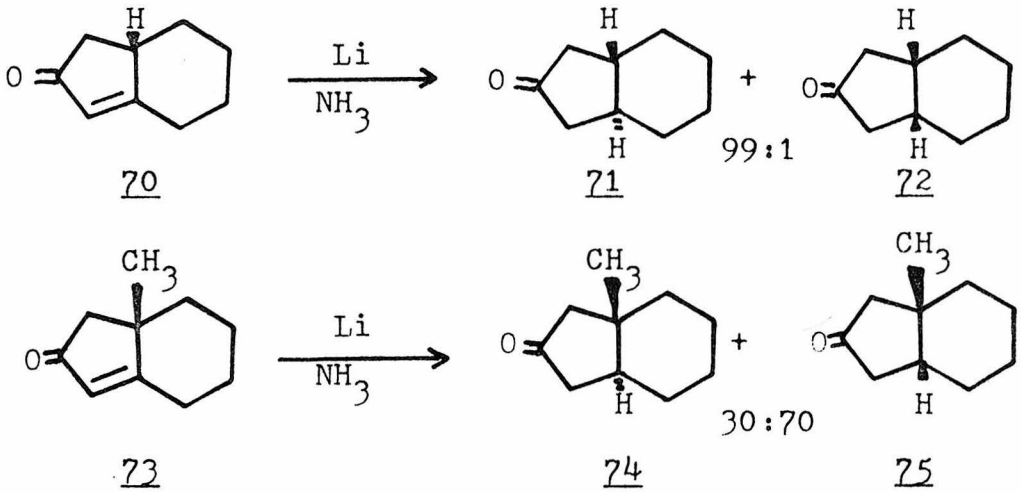
W-3 : R=H	HOAc, 3 atm. H_2 10% Pd/C	9:1	50%
W-4 : R=CH_3	HOAc, 3 atm. H_2 10% Pd/C	-	0% (92% s. m.)

Chart W (continued)

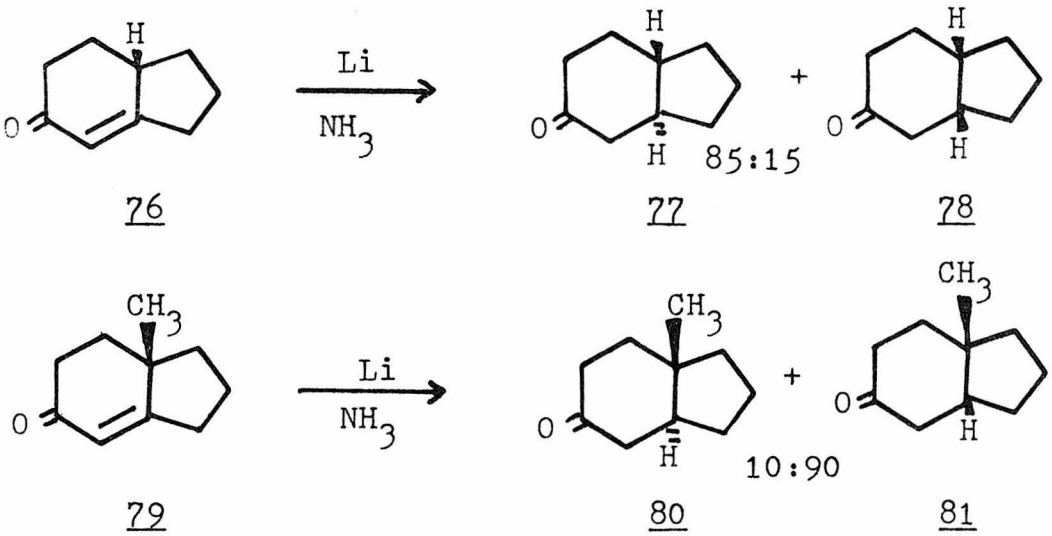


W-5

Na, NH_3, dioxane	87	13
Li, NH_3, dioxane	76	24
Ca, NH_3, dioxane	59	41
Ba, NH_3, dioxane	44	66
H_2, Pd/C, EtOH	11	89



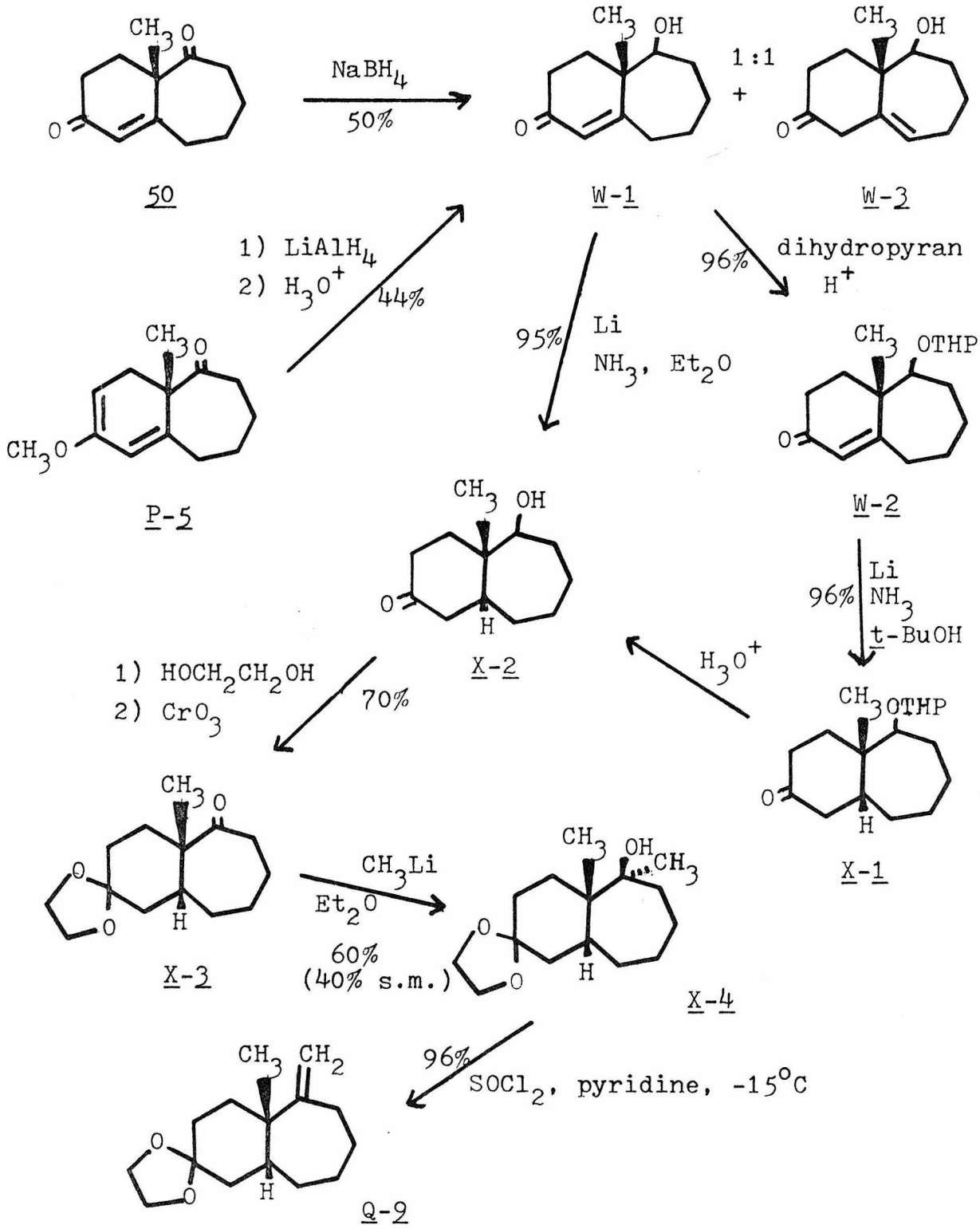
However, the reduction of the enone 73 led to a 30:70 ratio of trans-fused system 74 to cis-fused system 75. Similarly, while the reduction of hydroindanone 76 gave an 85:15 ratio of 77:78, the reduction of 79 afforded a 10:90 ratio of 80:81 (74).



More of the trans-fused material was available by hydrogenation. For example, hydrogenation of W-1 in acetic acid at either one or three atmospheres pressure afforded a 2:1 ratio of cis- to trans-material. Moreover, hydrogenation of W-1 in base gave a 3:2 ratio of cis- to trans-fused material. Now the bridgehead methyl is inhibiting hydrogenation from the beta face since the hydrogenation of W-5 gave mainly cis-fused material (59). However, hydrogenation of Q-2 in acetic acid gave only cis-fused material. Now the alpha methyl group at C-10 prevents any hydrogenation from the alpha face. The best trans- to cis-fused ratio (9:1) came from the hydrogenation of the deconjugated material W-3; however the yield was low, and similar hydrogenation of compound W-4 (with the alpha methyl at C-10) gave back only starting material. Evidently, olefin W-4 is now hindered to hydrogenation from both faces of the molecule.

Chart X shows the synthesis of the ketones W-1, W-2, and W-3, and correlation with the exocyclic olefin Q-9. Note that the reduction of homo-Wieland-Miescher ketone (50) afforded both conjugated and unconjugated keto alcohols W-1 and W-3. (As shown in Chart I, reduction of Wieland-Miescher ketone gave cleanly the α,β-unsaturated ketone I-1). Also, ketone X-3 was much more sterically hindered than the corresponding trans-fused six-membered ring ketone I-6, since treatment of ketone X-3 with six equivalents of

Chart X


NaBH4
50%
1:1
+
50
W-1
W-3
1) LiAlH4
2) H3O+
44%
95%
Li
NH3, Et2O
96%
dihydropyran
H+
P-5
W-2
96%
Li
NH3
t-BuOH
H3O+
X-2
1) HOCH2CH2OH
2) CrO3
70%
X-1
X-3
CH3Li
Et2O
60%
(40% s.m.)
X-4
96%
SOCl2, pyridine, -15°C
Q-9

methyllithium afforded substantial amounts of starting material (whereas ketone I-6 was completely reduced with 1.5 equivalents of methyllithium).

It appeared that the synthesis was in trouble since aphidicolin has a trans-fused A/B ring. However, it is known that in steroids when the A/B ring is cis-fused, thermodynamic enolization of ketones at C-3 is almost exclusively towards the four position. This is because of the relief of nonbonded steric interactions between the C-4α and the C-7α and C-9α hydrogens when a trigonal center is formed at C-4 (75). Hence, it was hoped that the cis-fused system in the aphidicolin synthesis would behave similarly so that a suitable intermediate (after the solvolysis) could be brominated and dehydrobrominated to reintroduce the Δ^4 double bond which had been removed during the reduction of enone Q-2. Therefore, H_2 would be acting as a protecting group for a double bond! Overall, this was just as efficient as the original synthesis for a trans-fused system which called for the introduction of a Δ^1 double bond as a blocking group for enolization toward the two position (see Chart V).

The other major problem with the synthesis at this point was that after the ring contraction the aphidicolin series was always contaminated by ever increasing amounts of the stemodin series, and the two series could not be easily separated. This problem was solved (see Chart Y)

Chart Y

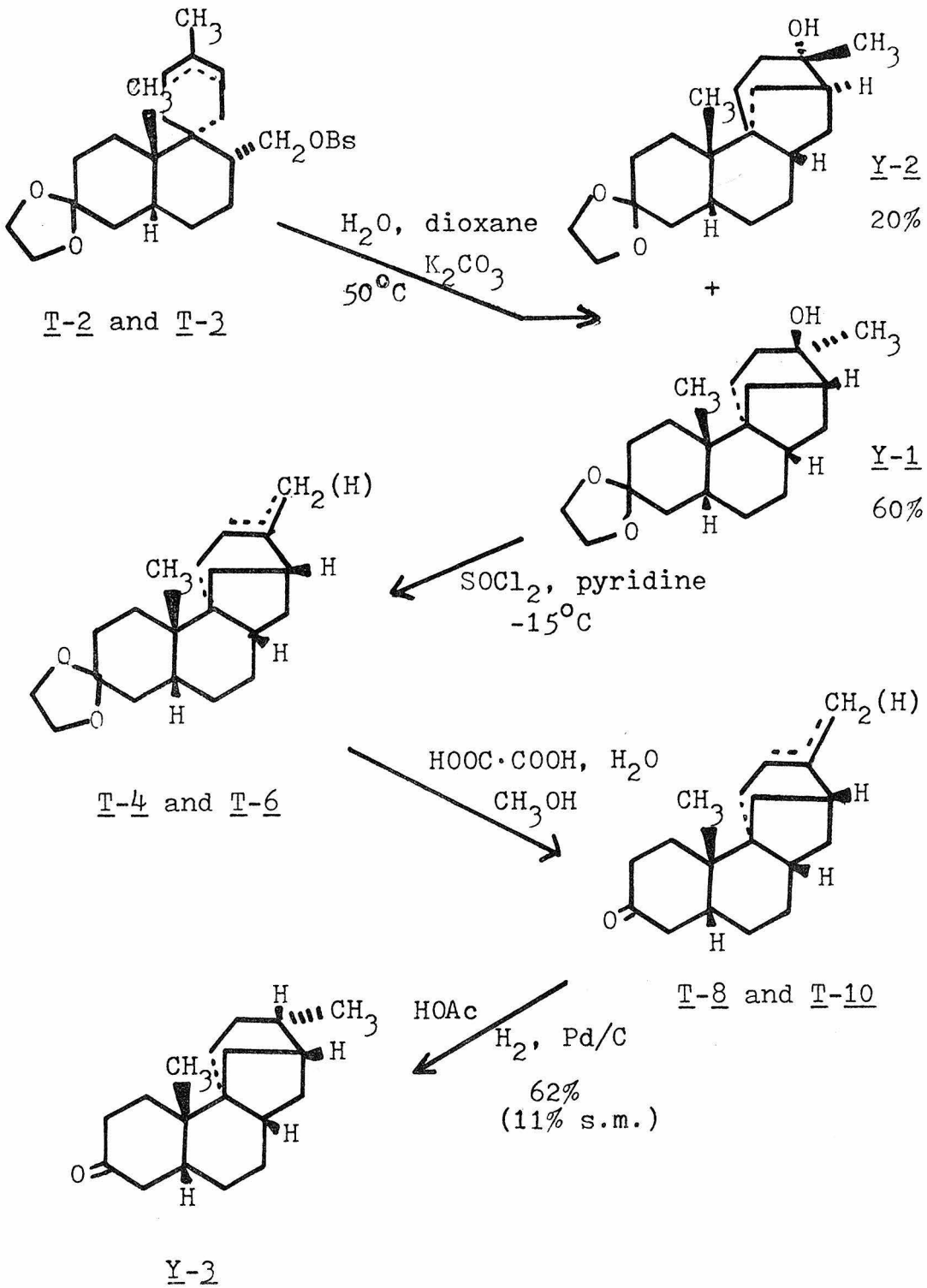
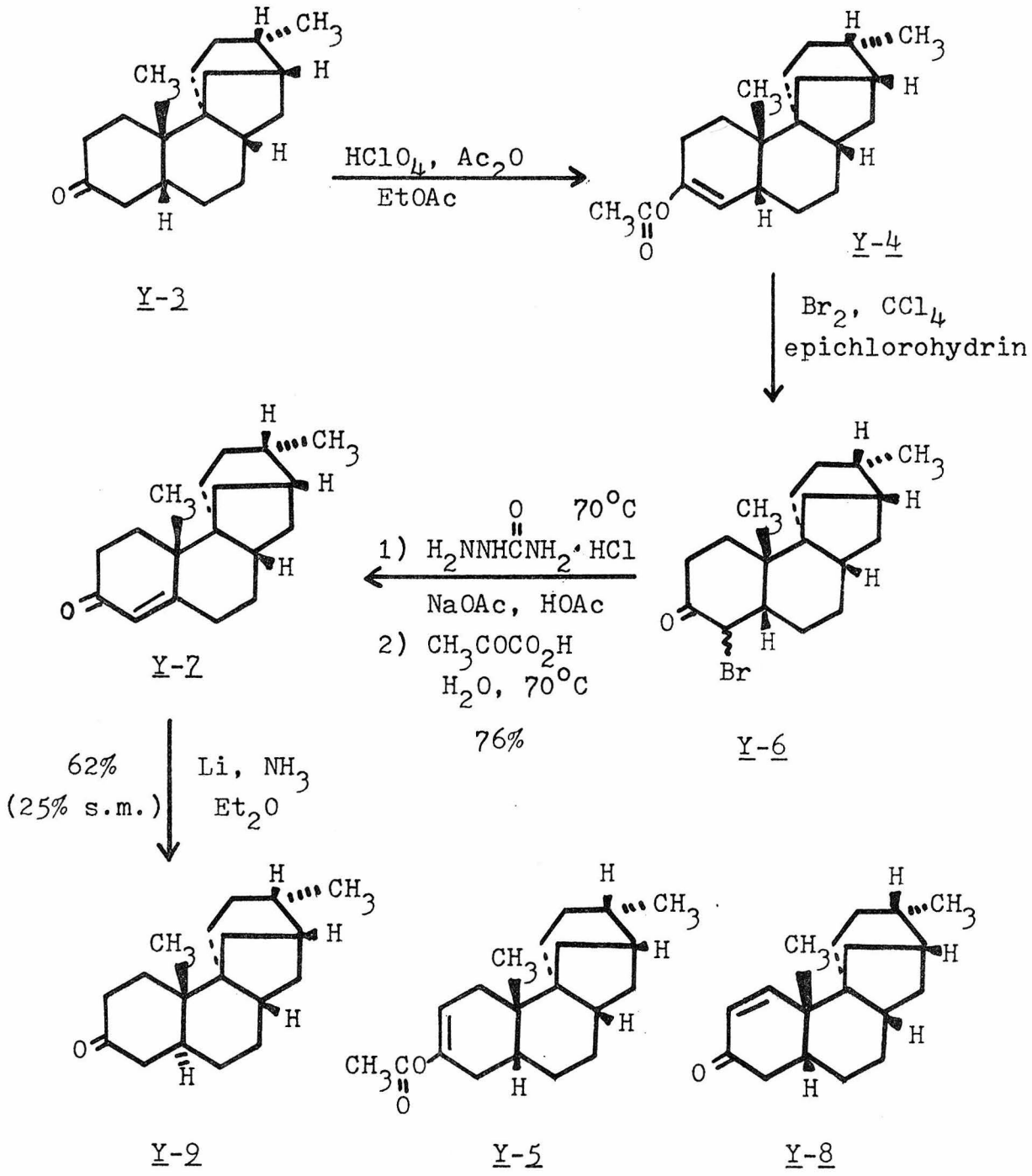

T-2 and T-3
H2O, dioxane
K2CO3
50°C
Y-2
20%
+
Y-1
60%
SOCl2, pyridine
-15°C
T-4 and T-6
HOOC·COOH, H2O
CH3OH
T-8 and T-10
HOAc
H2, Pd/C
62%
(11% s.m.)
Y-3

Chart Y (continued)



by doing the solvolysis of brosylates T-2 and T-3 in water and dioxane to give the alcohols Y-1 and Y-2. The two alcohols were easily separated on silica gel to give about 60% of the desired alcohol Y-1 (eluted first) and 20% of the alcohol for the stemodin series Y-2. The stereochemistry as shown represents axial attack by hydroxyl from the least hindered side of the bicyclo[3.2.1]-octane system. It also represents backside attack by hydroxyl if the solvolysis takes place in a somewhat concerted fashion with the carbonium ion being attacked as soon as it begins to be formed (76).

Now the goal was to test the efficacy of the proposed A ring synthesis. To avoid complications by reactions in the D ring all functionality was removed by first dehydration of the alcohol Y-1 with thionyl chloride in pyridine to give a mixture of endocyclic and exocyclic olefins T-4 and T-6. The ketals were then hydrolyzed and the ketones T-8 and T-10 hydrogenated in acetic acid at atmospheric pressure to furnish the saturated ketone Y-3 in overall 62% chromatographed yield (plus 11% starting olefins) from the alcohol. The stereochemistry shown represents hydrogenation of the D ring from the top face, i.e. the least hindered face of the molecule. Thermodynamic enolization (77) gave only one enol acetate Y-4, and bromination in carbon tetrachloride with epichlorohydrin as a scavenger for HBr (78) followed by dehydrobromination via a Mattox-

Kendall reaction (79) afforded only one UV active material, Y-7, with chromatographed yield (from Y-3) of 76%. Since none of enone Y-8 was isolated, there was probably little or no enolization toward the two position to give enol acetate Y-5. The crucial reduction of enone Y-7 (with lithium in ammonia) afforded the desired trans-fused ketone Y-9 in 62% chromatographed and crystallized yield. About 25% starting material Y-7 was also recovered since no proton source such as t-butanol was added (because the reaction was being done on less than a 0.10 mmol scale). Less than 5% of the cis-fused material Y-3 was formed. The two compounds, though identical by VPC, had different TLC (Y-3 being more polar) behavior. Also, the NMR shift of the bridgehead methyl in Y-9 was 0.19 ppm downfield from that of Y-3. Finally, the trans-fused ketone Y-9 was highly crystalline (even the crude 60% pure material crystallized), while Y-3 was not.

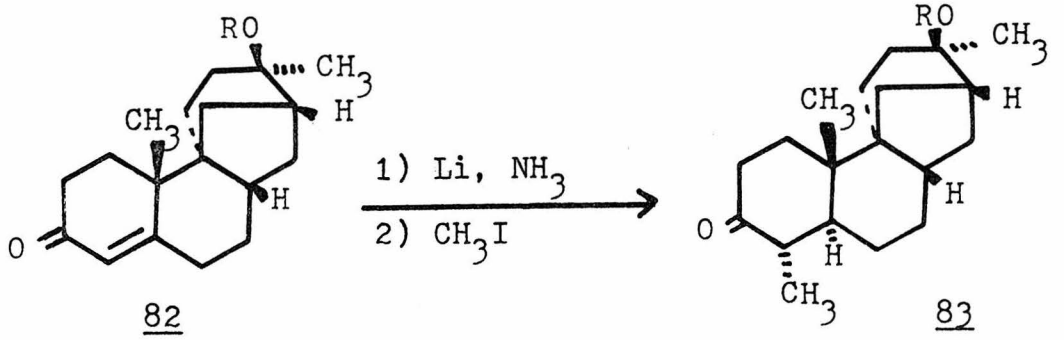
Thus the prognosis for the total synthesis of d,l-aphidicolin using the spiroannelation, ring contraction, and intramolecular solvolysis approach appears good. The construction of tetracyclic alcohol Y-1 involves 19 steps with an overall yield from 2-methoxybenzosuberone of about 3% (an average yield of 83% per step). Only two chromatographies with any degree of difficulty are required (one after the ring contraction and one after the solvolysis) and both of these are relatively late in the synthesis.

The rest of the intermediates are purified mainly by distillation, fractional crystallization, or column filtrations. Although two recyclings are necessary (of the exocyclic olefin Q-9 from the dehydration step and of the spiro ketone R-7 after the oximo ketone formation), there is no significant loss of material in either of these steps, and, in fact, the step with the lowest yield (50%) is the very first one in the synthesis. Also, it is possible to reintroduce the Δ^4 double bond after the solvolysis and generate the desired trans A/B ring fusion. Furthermore, compound Y-9 contains all of the asymmetric centers as in aphidicolane (3) and only requires the introduction of the two methyl groups at C-4. The overall yield of the tetracyclic Y-9 from 2-methoxybenzosuberone is about 1% and involves 26 separate steps (84% yield per step).

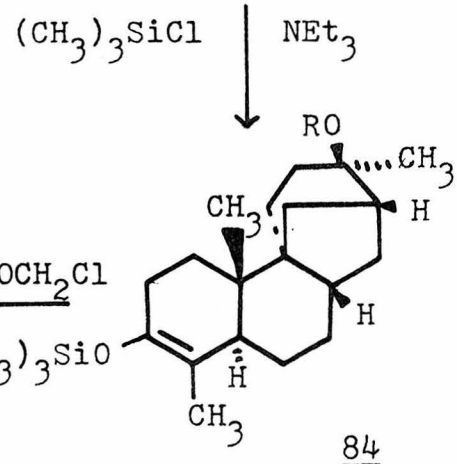
Conclusion

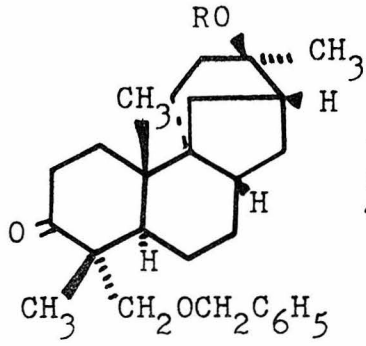
The synthetic studies undertaken thus far demonstrate a feasible approach to α,ℓ-aphidicolin. Six of the seven asymmetric centers in aphidicolin have been constructed, and all appear to have the proper configuration. The main problem that remains is to build the A ring with proper orientation of the methyl and hydroxymethyl groups at C-4.

Several approaches to the A ring are possible using the intermediate Y-1. For example, the double bond could be introduced as in Chart Y to give compound 82 (R is either hydrogen or a protecting group such as benzyl or trimethylsilyl). Reduction of 82 with lithium in ammonia followed



82 83

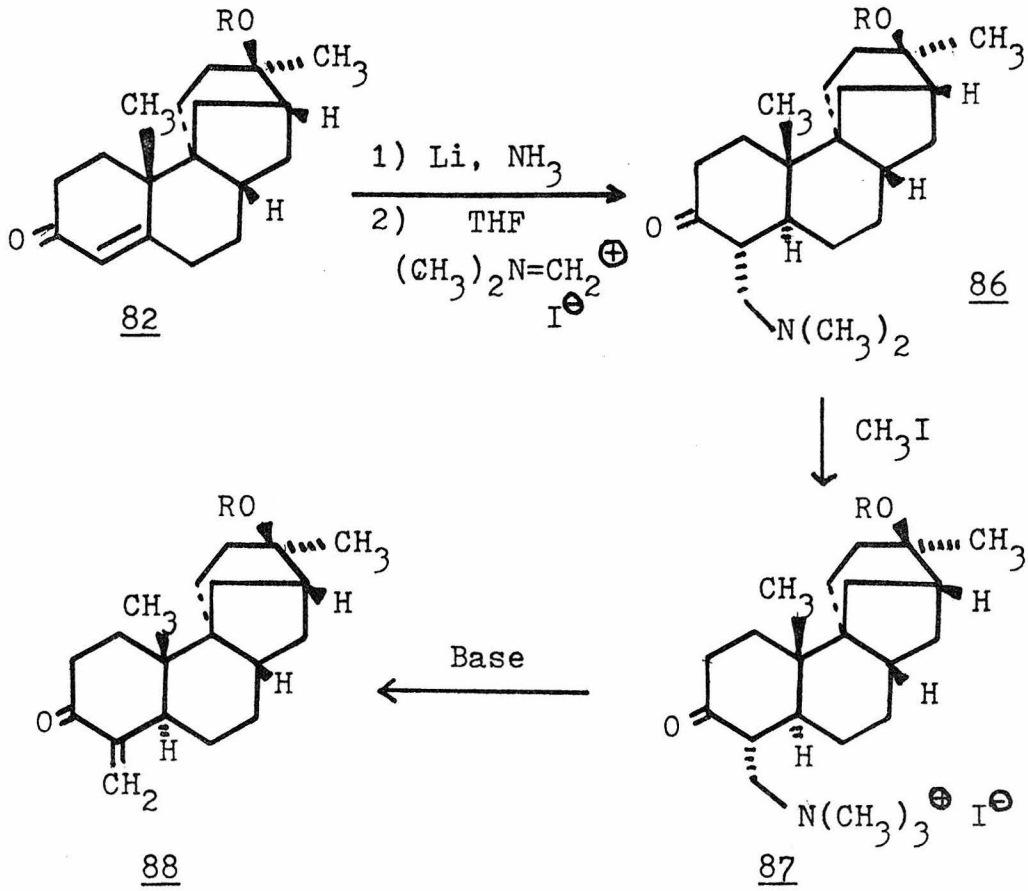




84 85

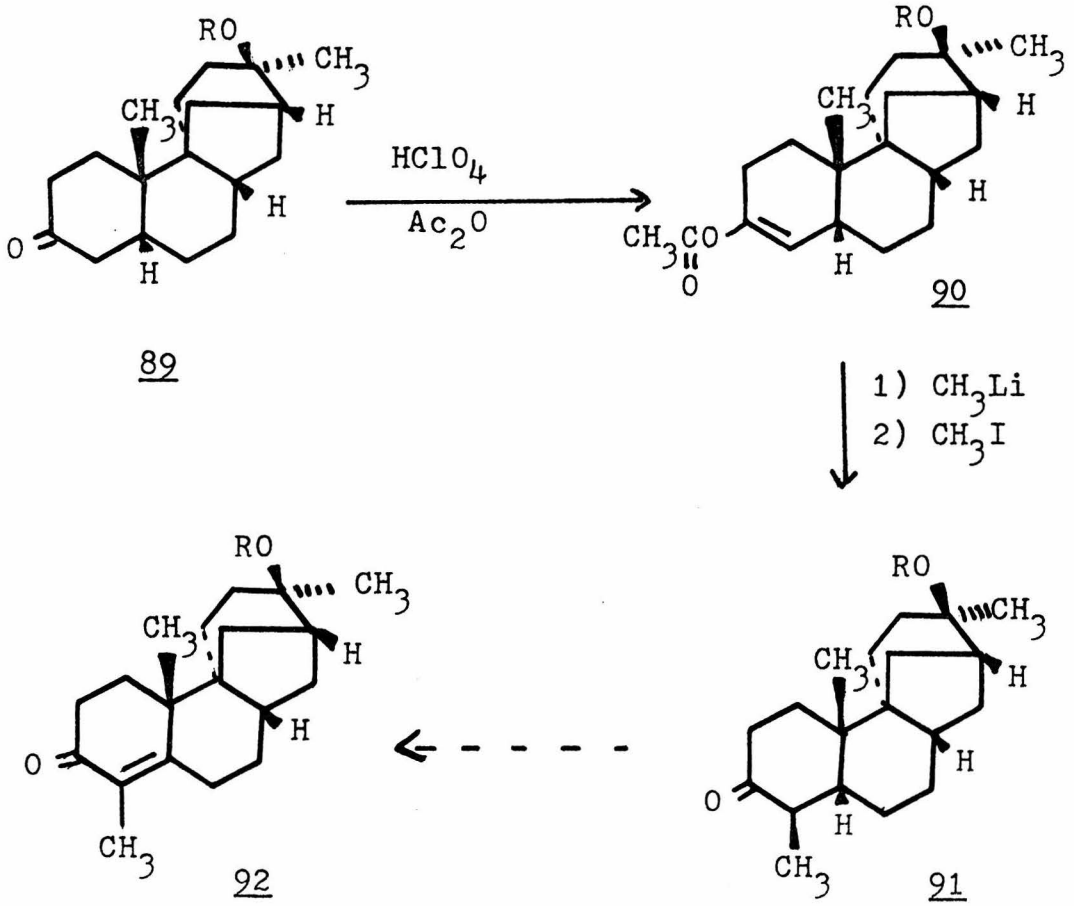
by trapping of the enolate with methyl iodide should furnish ketone 83. The thermodynamic enol ether 84 (80) can then be cleaved and the regiospecific enolate (73) trapped with chloromethyl benzyl ether (81). Because of steric hindrance of the bridgehead methyl at C-10, the second group introduced (the benzyl ether) should approach from the alpha face to give the stereochemistry of 85 as shown (82).

Another possibility is to trap the enolate resulting from the reduction (by lithium in ammonia) of 82 with dimethyl(methylene)ammonium iodide (83) to give the Mannich product 86. Conversion to the methiodide followed by treatment with base should give the methylene ketone 88 (84).



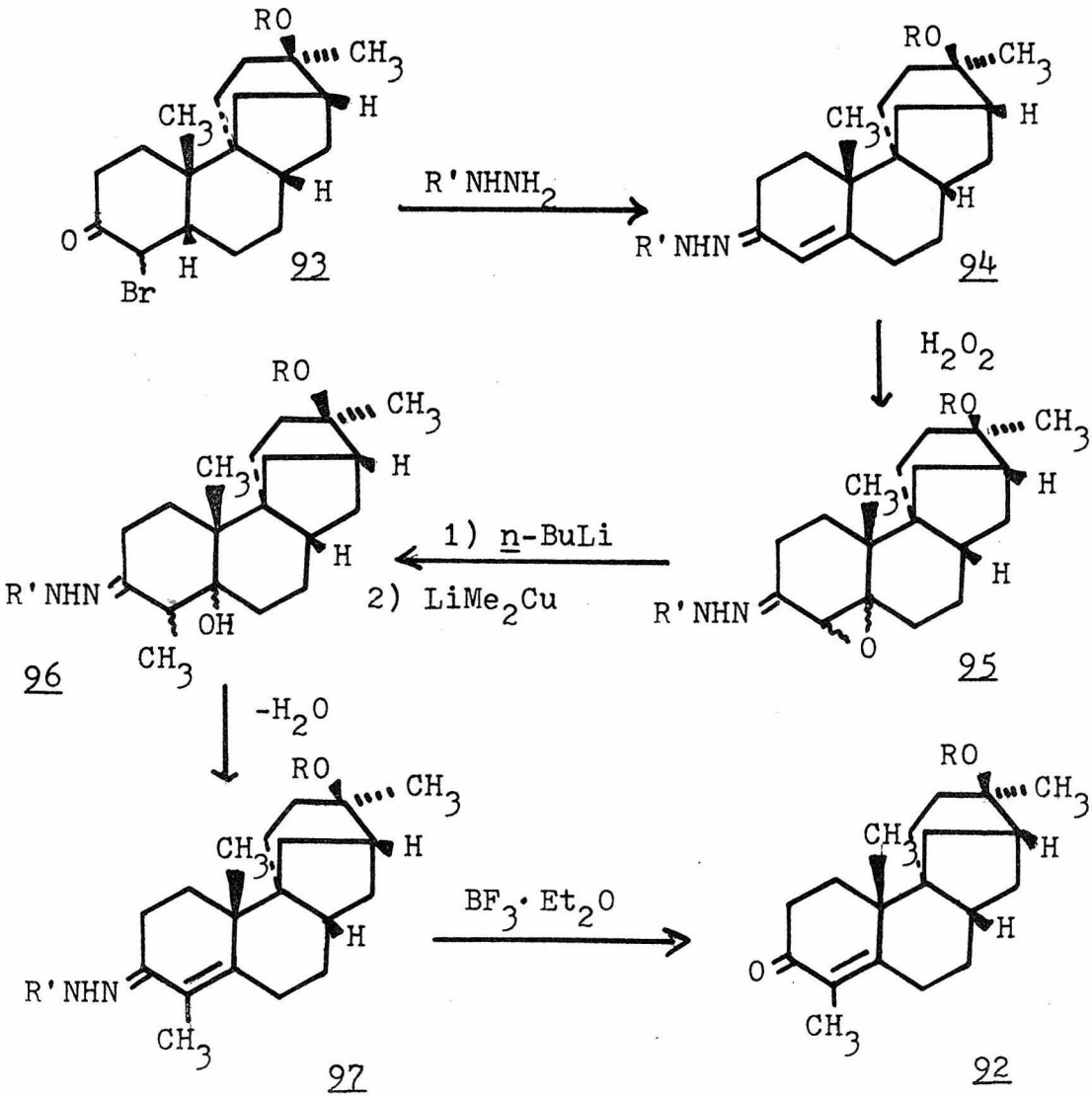
Compound 88 can then be reduced with lithium in ammonia and the enolate trapped with chloromethyl benzyl ether to afford compound 85 as before.

An alternate approach also utilizes the cis-fused A/B ring material Y-1. Ketone 89 is enolized under thermodynamic conditions to give enol acetate 90. Cleavage of enol acetate 90 with two equivalents of methyl lithium and trapping with methyl iodide should furnish ketone 91 (85). Compound 91 can be converted into enone 92 as in Chart Y. The enone 92 can be reduced with lithium in ammonia and alkylated with chloromethyl benzyl ether to give 85.



89 90 91 92

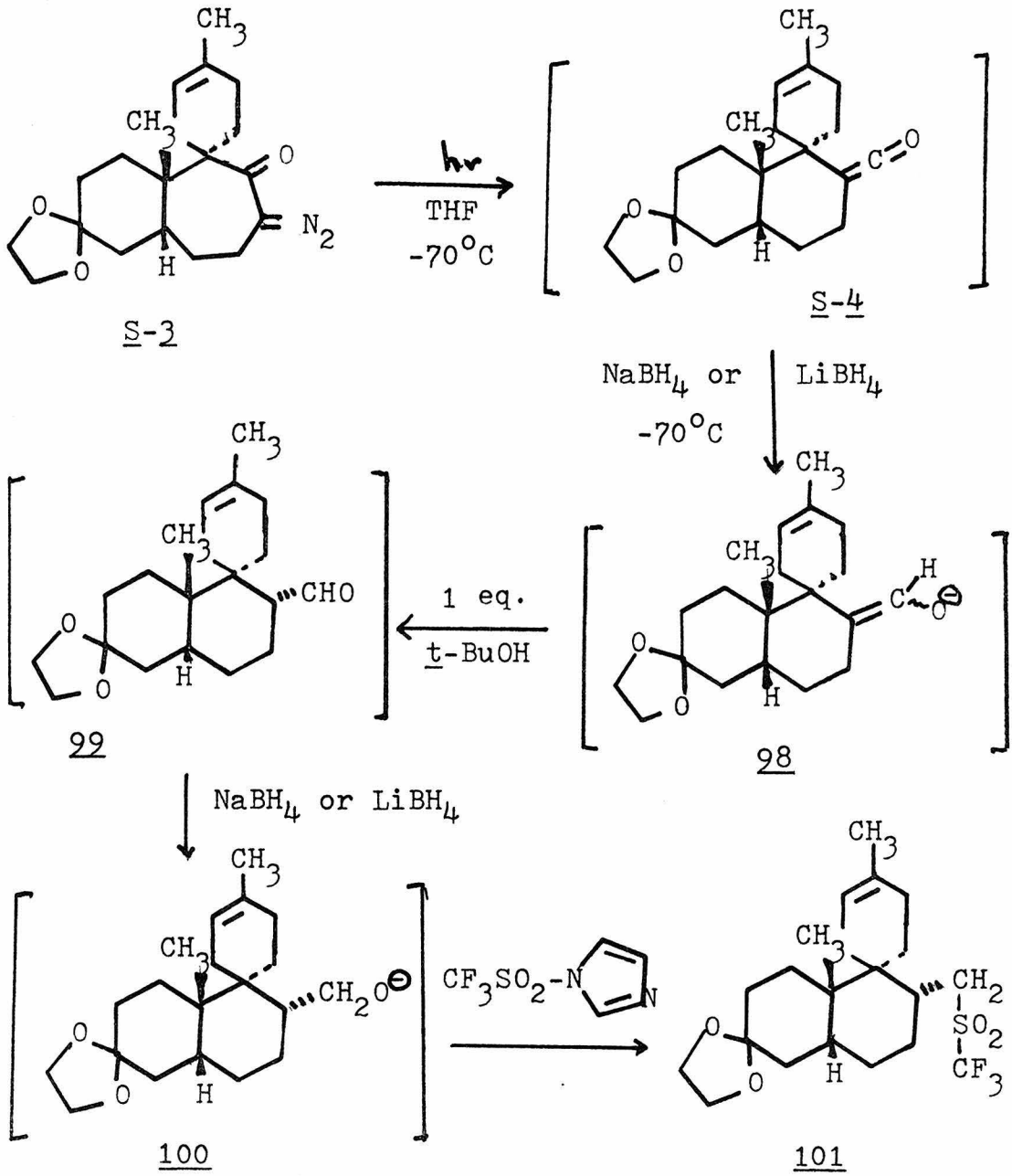
A novel approach to the A ring involves the work of Fuchs (86) and Stork (87). The α,β-unsaturated hydrazone 94 (the product of the Mattox-Kendall reaction on 4-bromo-ketone 93) could be epoxidized to produce the compound 95. Treatment of the hydrazone 95 with base and then lithium dimethyl cuprate should give the alcohol 96. Elimination of water affords olefin 97. Hydrolysis should give the enone 92 which can then be reduced and alkylated as before to give the desired ketone 85.



Probably the most efficient approach (see Chart Z) to the A ring of aphidicolin is to introduce the methyl group at C-4 by trapping the enolate during the reduction of enone Q-2 with methyl iodide to give the methyl ketone Z-1. Hence, regeneration of the Δ^4 double bond later in the synthesis should give enone 92 directly. After reductive alkylation of enone 92 to give compound 85, the axial alcohol at C-3 could be produced by the reduction of ketone 85 with lithium tri-sec-butylborohydride (88).

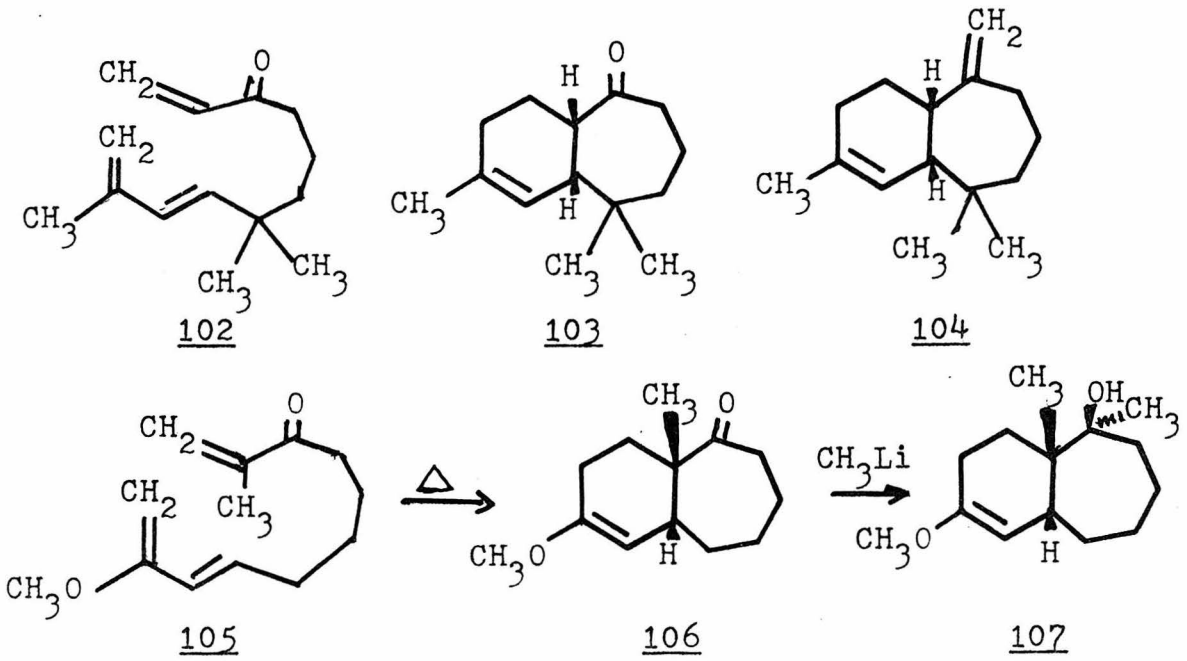
The present approach to aphidicolin suffers somewhat in that between the ring contraction and solvolysis steps isomerization of the olefin in the spiro ring takes place. While much of the isomerization appears to occur during the reduction of the ester S-6 (see Chart S) to the alcohol S-8, some olefin isomerization takes place during the formation and solvolysis of brosylate T-2 (Chart T). Although isomerization at each step is less than ten percent, it becomes a more serious problem as the synthesis proceeds. One possible idea to minimize the problem is to perform the solvolysis on the triflate 101 (89). The triflate should be much more labile and solvolyze under much milder conditions than the brosylate. (It may in fact solvolyze at or below room temperature to give the exocyclic olefin T-6). A further plan to circumvent the isomerization problem is to perform the Wolff rearrangement in such a manner so as to produce the triflate directly. For example, the

ketene S-4 (stable to methanol and to intramolecular cycloaddition at -70°C) can be treated in situ with sodium borohydride or lithium borohydride and one equivalent of a proton source (such as t-butanol) at or below -70°C, let warm slowly, and the resulting alcoholate 100 trapped in situ with trifluoromethanesulfonic imidazolide.



The 25 step synthesis in Chart Z represents a possible approach to aphidicolin. The last few transformations involve the formation of the D ring via kinetic elimination of the alcohol (R=H) or suitable leaving group ($R=CH_3\overset{O}{\overset{\|}{C}}-$) to form the exocyclic olefin. Hydroxylation of the olefin from the least hindered side of the molecule using osmium tetroxide should furnish the desired diol for aphidicolin.

A completely different approach to compound Z-1 involves the use of an intramolecular Diels-Alder reaction of a suitable acyclic precursor 105. A similar Diels-Alder reaction of 102 to give the bicyclic ketone 103 was used in a synthesis of α-himachalene (104) (90). The methyl enol ether 107 can be cleaved with lithium diphenylphosphide (91) and the regiospecific enolate trapped with methyl iodide to give the desired ketone Z-1.



102 103 104

105 106 107

Chart Z

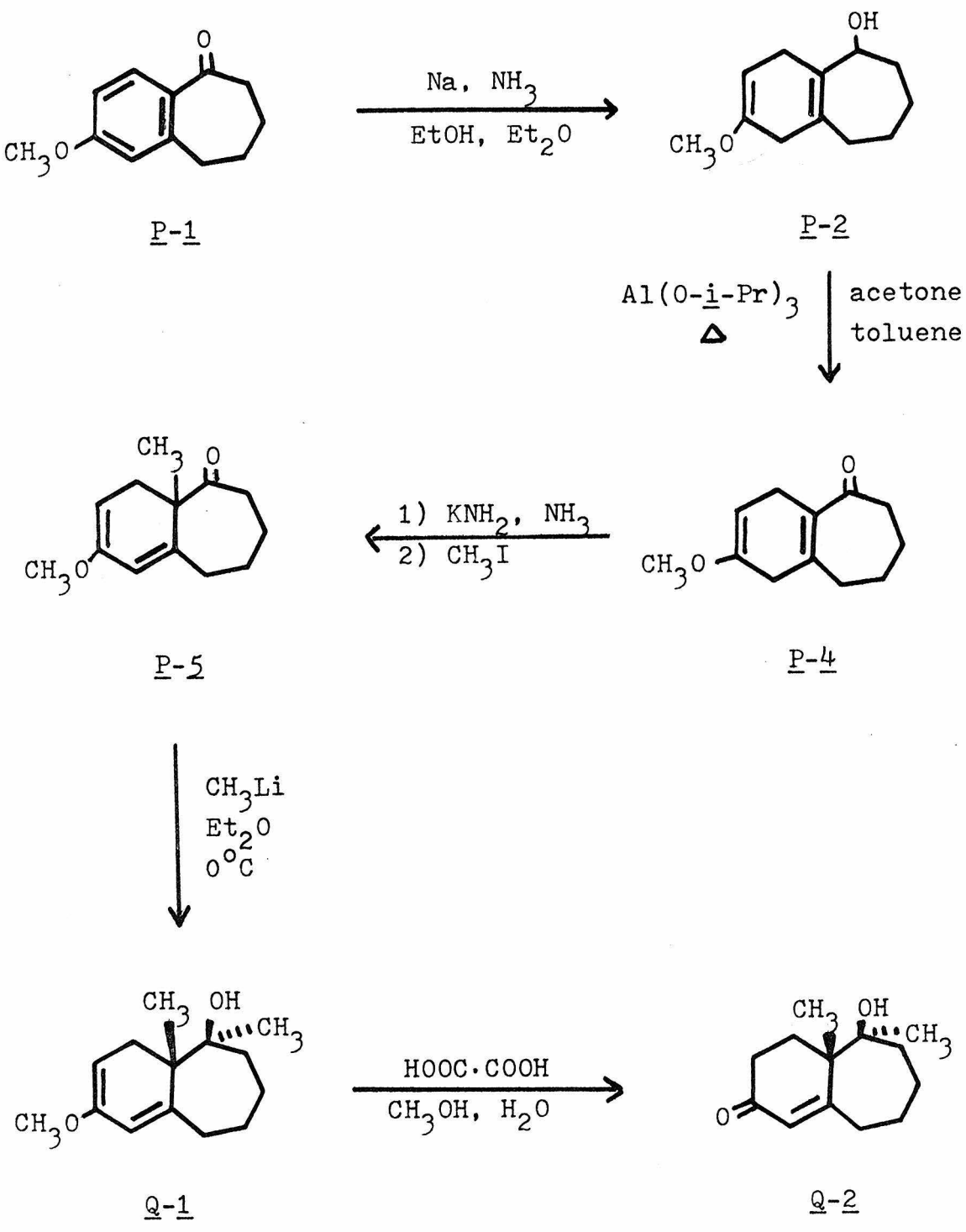
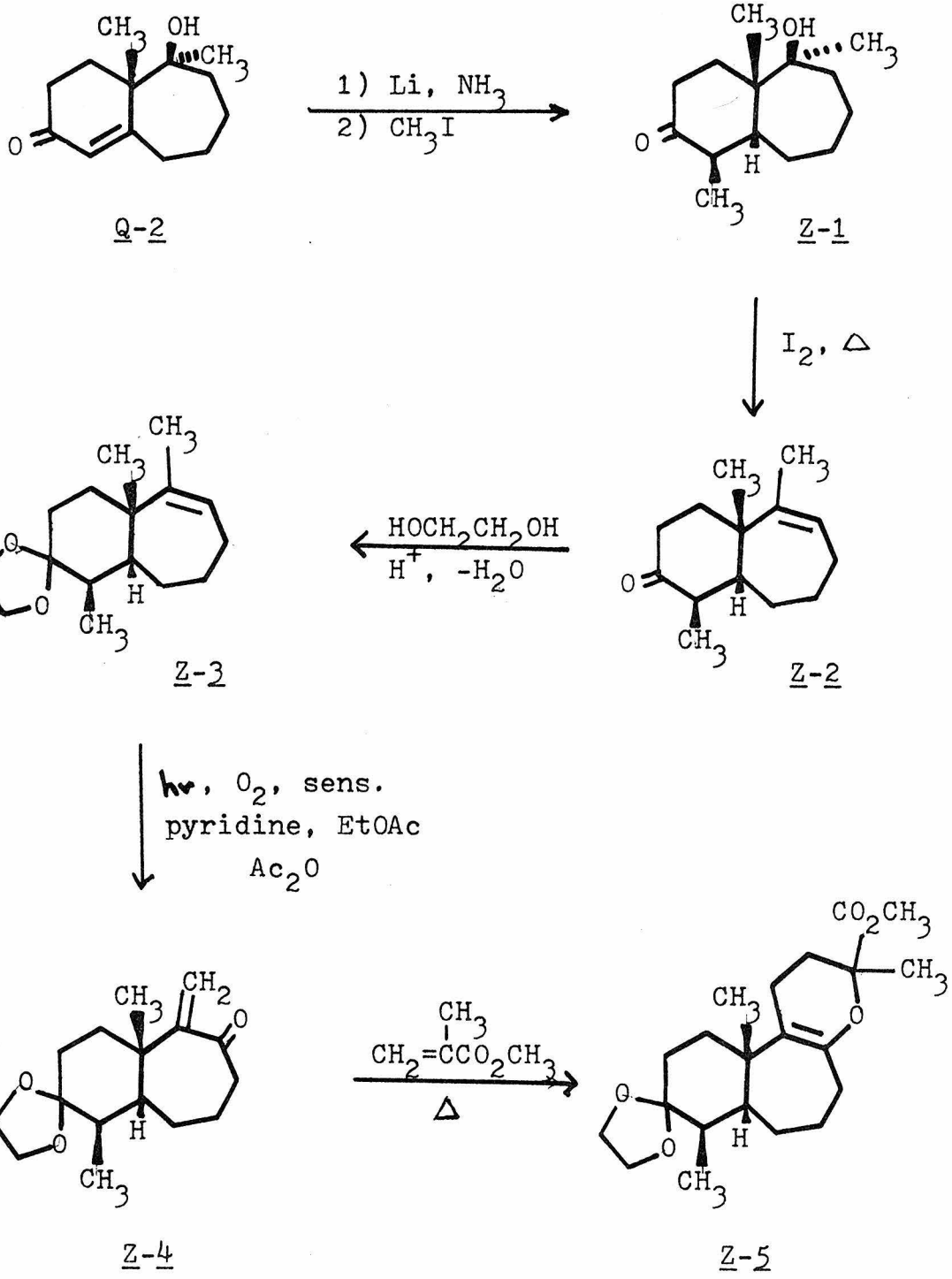

O
CH3O
Na, NH3
EtOH, Et2O
OH
CH3O
P-1
P-2
Al(O-i-Pr)3
Δ
acetone
toluene
CH3
O
CH3O
1) KNH2, NH3
2) CH3I
O
CH3O
P-5
P-4
CH3Li
Et2O
0°C
CH3
OH
CH3
CH3O
HOOC·COOH
CH3OH, H2O
CH3
OH
CH3
O
Q-1
Q-2

Chart Z (continued)



Q-2 Z-1 Z-2 Z-3 Z-4 Z-5

Chart Z (continued)

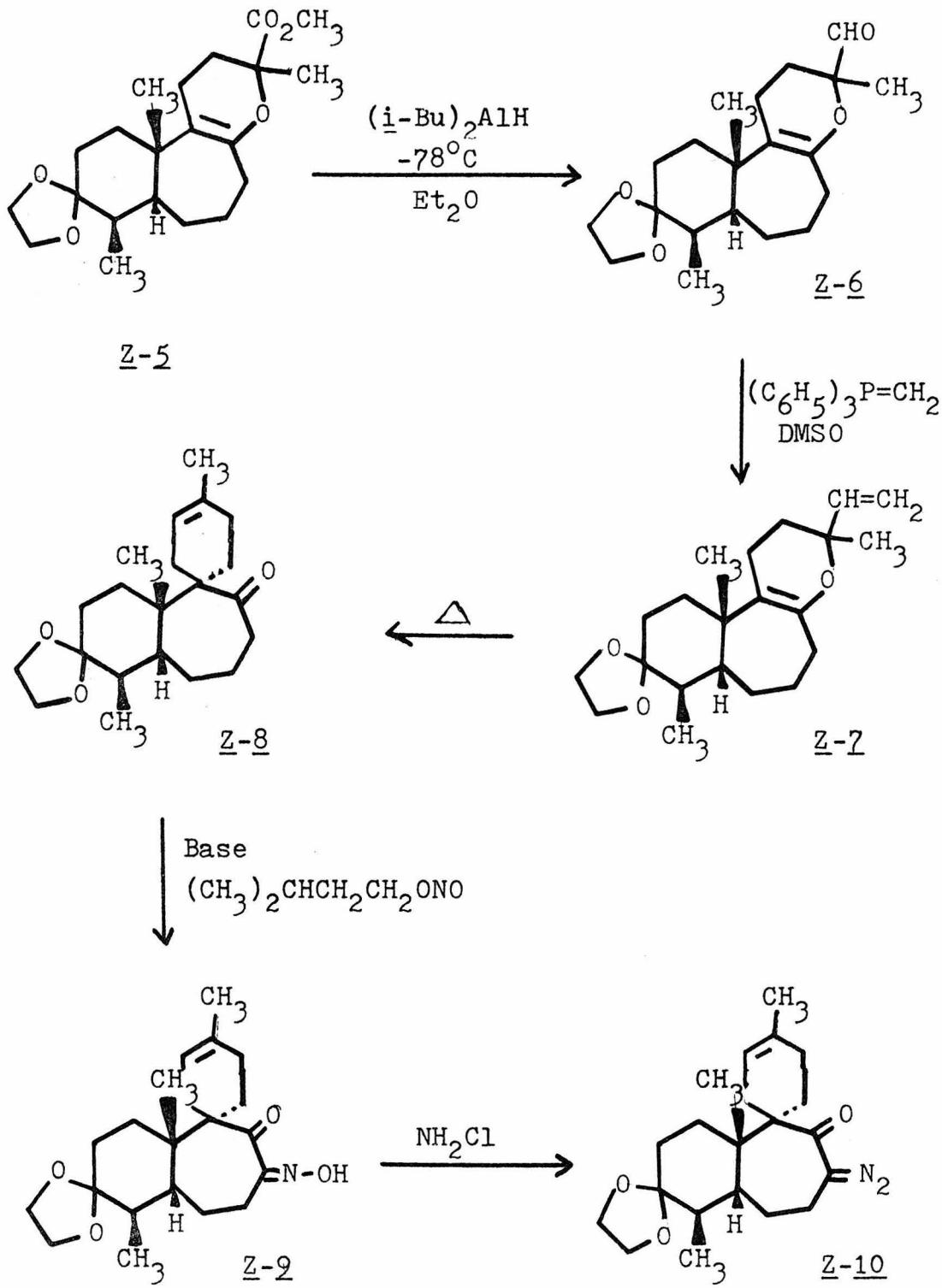
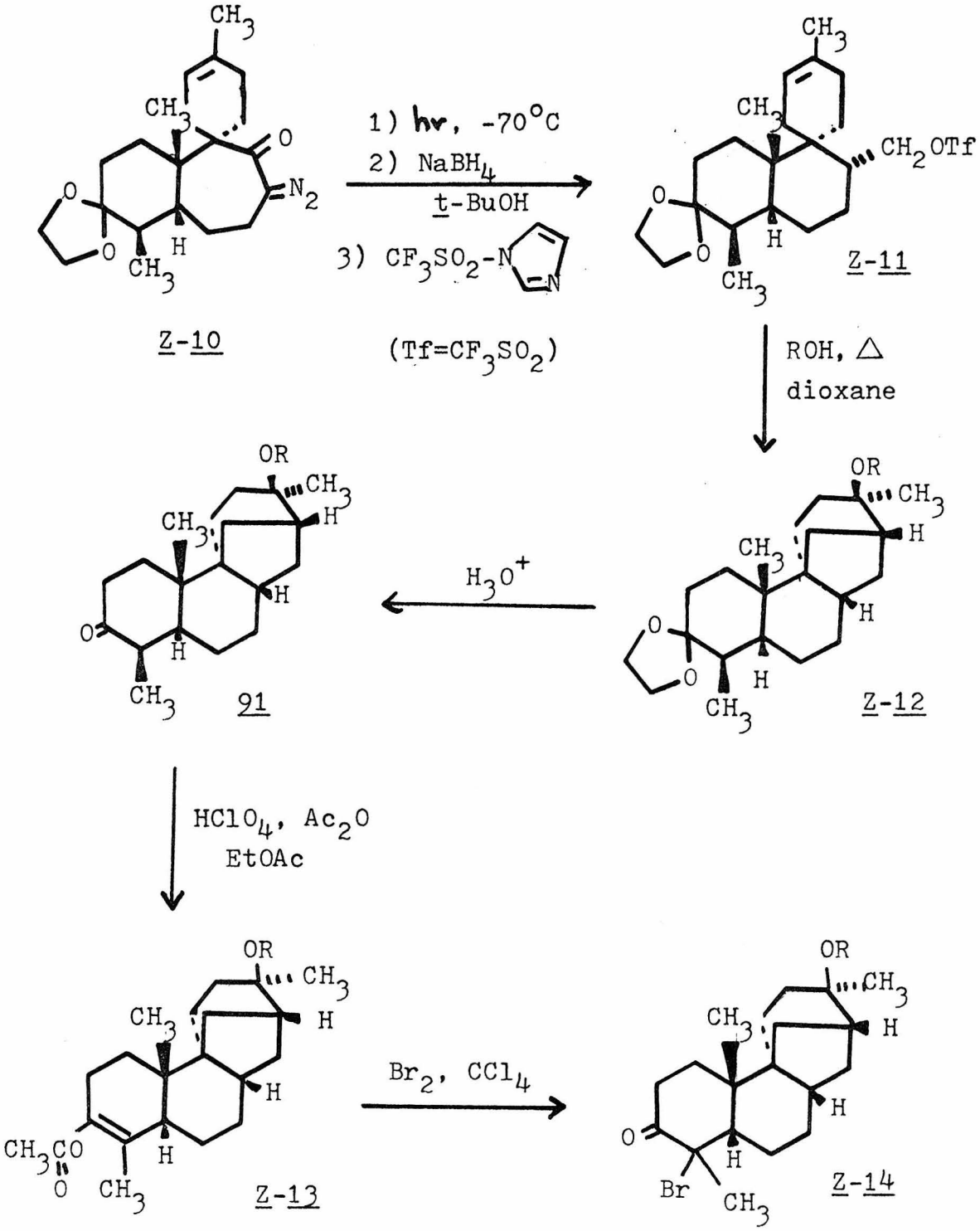
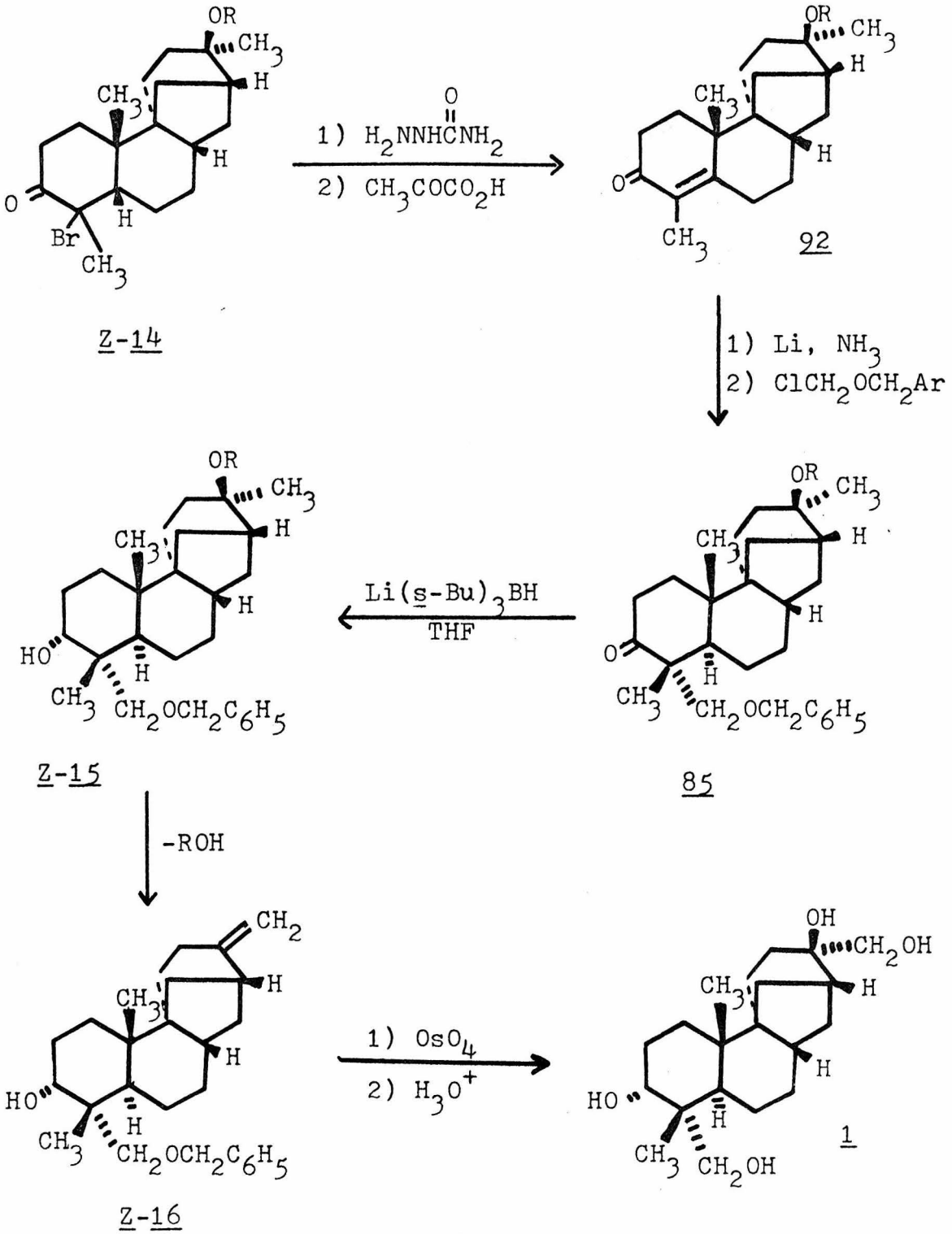


Chart Z (continued)



Z-10 Z-11 Z-12 91 Z-13 Z-14

Chart Z (continued)



Experimental Section (92)

Melting points labeled (vacuum) were taken in evacuated capillaries on a Hoover capillary melting point apparatus, while all others were determined on a Kofler micro hot stage melting point apparatus. All melting points and boiling points are uncorrected. Infrared (ir) spectra were determined on a Perkin-Elmer 237B grating infrared spectrometer, and nuclear magnetic resonance (nmr) spectra were recorded using either a Varian T-60 or Varian A-60 spectrometer. Chemical shifts are reported as δ values in parts per million relative to tetramethylsilane (δ_{TMS} 0.0 ppm) as an internal standard.

Gas-liquid phase chromatographic (vpc) analyses were determined on a Hewlett-Packard 5750 gas chromatograph using helium carrier gas at a flow rate of 60 ml/min. All analytical vpc was conducted on a 5 ft x 0.125 in. column packed with 4% SE-30 on 60-80 mesh Chromosorb WAW DMCS.

Preparative layer chromatography (ptlc) was carried out on pre-coated PLC plates with a 20x20x2mm layer of silica gel 60F-254 on glass plates manufactured by E. Merck, Darmstadt, Germany.

Alumina used for chromatography refers to the grade I, neutral variety manufactured by M. Woelm, Eschwege, Germany made up to grade II or III as indicated by addition of 3% or 6% water prior to use. Silica gel columns used the

0.05-0.2 mm silica gel manufactured "for column chromatography" by E. Merck and Co., Darmstadt, Germany. Preparative medium-pressure column chromatography was performed using 1/2 x 20 in. or 2 x 20 in. glass columns with fittings supplied by Chromatronix, Inc., Berkeley, Ca., and an instrument minipump supplied by Milton Roy Co., St. Petersburg, Fl. The columns were packed with silica gel H "for tlc acc. to Stahl" (10-40) manufactured by E. Merck and Co., Darmstadt, Germany. Ether and petroleum ether were degassed under water aspirator vacuum prior to use.

"Dry" solvents were dried immediately prior to use. Ether and tetrahydrofuran were distilled from lithium aluminum hydride; t-butanol, pyridine, and benzene distilled from calcium hydride; dichloromethane and iodomethane were distilled from phosphorous pentoxide; methanol was distilled from magnesium turnings. "Ether" refers to anhydrous diethyl ether which is supplied by Mallinckrodt Co., St. Louis, Mo. "Petroleum ether" refers to the "Analyzed Reagent" grade hydrocarbon fraction, bp 35-60°, which is supplied by J. T. Baker Co., Phillipsburg, N.J., and was not further purified.

All water used in the reactions and workups was distilled water. Brine refers to a saturated aqueous solution of sodium chloride. Bicarb refers to a saturated aqueous solution of sodium bicarbonate. "Concentration of solvents in vacuo" refers to solvent renewal under reduced

pressure (water aspirator) using a rotary evaporator at or below 30°. "Removal of solvents *in vacuo*" refers to first solvent renewal under reduced pressure (water aspirator) using a rotary evaporator at or below 30°, then drying the residue *in vacuo* at 1 mm pressure for several hours at room temperature.

All reaction flasks and syringes were dried for at least twelve hours in an oven (at 140°) and cooled in a dessicator over anhydrous calcium sulfate prior to use. All reactions (except the photooxygenations and hydrogenations) were run under an atmosphere of argon, and at the beginning of all reactions, the solutions were degassed.

Mass spectral analyses were performed by Ms. Beth Irwin, UCLA, Los Angeles, Ca. Microanalyses were performed by Spang Microanalytical Laboratory, Ann Arbor, Michigan. X-ray analyses were performed in the laboratories of Professor Jon Bordner, University of North Carolina, Raleigh, North Carolina.

8,8(7H)-Ethylenedioxy-3β-methoxycarbonyl-3α,10aβ-dimethyl-2,3,5,6,6aα,9,10,10a-octahydro-1H-naptho[2,1-b]pyran (J-1) and 8,8(7H)-ethylenedioxy-3α-methoxycarbonyl-3β,10aβ-dimethyl-2,3,5,6,6aα,9,10,10a-octahydro-1H-naptho[2,1-b]pyran (J-2)

A solution of 3.55 g (15.0 mmoles) of the methylene ketone H-8 (35) in 16.0 ml (15.1 g, 151 mmoles) methyl methacrylate (freshly distilled over CaH_2 and stabilized with 0.5% hydroquinone) in a base washed and oven dried tube was degassed under argon, sealed under vacuum, and heated for 22 hours at 180°C. Upon cooling, the viscous liquid was dissolved in 8 ml of chloroform; 100 ml of ether was added, the solution heated for 15 minutes on a steam bath, and filtered. The white precipitate was twice extracted with an additional 75 ml of diethyl ether. Solvents were removed in vacuo to give a yellow liquid which was chromatographed (medium pressure) on silica gel with 1:1 petroleum ether:diethyl ether to afford 1.88 g (37%) of ester J-1 (R_f 0.25) and 2.17 g (43%) of ester J-2 (R_f 0.2). Ester J-1 was a white solid, mp 87.5°-90.5°: ir ($CHCl_3$) 1730 (C=O) and 1680 cm^{-1} (C=C); nmr ($CDCl_3$) δ 0.91 (3, s, C-10a CH_3), 1.41 (3,s,C-3 CH_3), 3.72 (s, 3, methyl ester), 3.92 (s, 4, ketal). One recrystallization from hexane and ether furnished an analytically pure sample, mp 89°-92°.

Anal. Calcd for $C_{19}H_{28}O_5$: C, 67.83; H, 8.39. Found: C, 67.76; H, 8.43.

Ester J-2 was a white solid, mp 82-89°: ir ($CHCl_3$) 1730 (C=O) and 1680 cm^{-1} (C=C); nmr ($CDCl_3$) δ 0.91 (s, 3, C-10a CH_3), 1.48 (s, 3, C-3 CH_3), 3.72 (s, 3, methyl ester), 3.92 (s, 4, ketal). Recrystallization from ether and hexane gave an analytically pure sample, mp 97.5-99°.

Anal. Calcd for $C_{19}H_{28}O_5$: C, 67.83; H, 8.39. Found: C, 67.90; H, 8.41.

8,8(7H)-Ethylenedioxy-3β,10aβ-dimethyl-2,3,5,6,6aα,9,10,10a-octahydro-1H-naptho[2,1-b]pyran-3α-carbaldehyde (J-4)

To a solution of 1.97 g (5.86 mmoles) of ester J-2 in 400 ml of dry ether at -78° was added dropwise 22.0 ml (17.8 mmoles) of 0.81M diisobutylaluminum hydride in benzene. After 20 minutes at -78°, the reaction was quenched with 4.2 ml absolute methanol, the acetone-dry ice bath removed, and the solution allowed to warm to room temperature; 400 ml of saturated sodium bicarbonate solution was added and the organic layer was separated. The aqueous layer was extracted three times with 300 ml portions of ether, and the combined organic layers washed with 500 ml bicarb and then 500 ml brine, and dried over anhydrous potassium carbonate. Solvents were removed in vacuo to give 1.79 g (100%) of a white solid. One recrystallization from hexane gave an analytically pure sample, mp 108-111°: ir ($CHCl_3$) 1735 (C=O) and 1674 cm^{-1}

(C=C); nmr ($CDCl_3$) δ 0.90 (s, 3, C-10a CH_3), 1.25 (s, 3, C-3 CH_3), 3.83 (s, 4, ketal), 9.5 (s, 1, aldehyde).

Anal. Calcd for $C_{18}H_{26}O_4$: C, 70.56; H, 8.55. Found: C, 70.45; H, 8.70.

8,8(7H)-Ethylenedioxy-3β,10aβ-dimethyl-3α-vinyl-2,3,5,6,6aα,9,10,10a-octahydro-1H-naptho[2,1-b]pyran (36)

To a solution of 1.00 g (23.8 mmoles) of 57% sodium hydride in mineral oil (washed two times with pentane) in 250 ml dry dimethyl sulfoxide (distilled over calcium hydride) was added 8.50 g (23.8 mmoles) of methyl triphenylphosphonium bromide. The resulting solution was stirred for one hour at room temperature after which 1.78 g (5.82 mmoles) of the crude aldehyde J-4 was added. After an additional 26 hours, the solution was added to 250 ml ether and 750 ml water. The organic layer was separated and the aqueous layer extracted three times with 250 ml portions of ether. The combined organic layers were washed with 250 ml water and then 250 ml brine, and dried over anhydrous potassium carbonate. Solvents were removed in vacuo and the resulting solid filtered through 5 g of silica gel with 50 ml of ether to remove most of the triphenylphosphite. Chromatography on silica gel with 3:1 petroleum ether:diethyl ether afforded 1.48 g (84%) of a white solid (R_f 0.27), mp 95-100°. One recrystallization from methanol gave

analytically pure material, mp 97.5-99.5°: ir ($CHCl_3$) 1680 cm^{-1} (C=C); nmr ($CDCl_3$) δ 0.95 (s, 3, C-10a CH_3), 1.30 (s, 3, C-3 CH_3), 3.93 (s, 4, ketal), 5.4 (complex multiplet, 3, vinyl hydrogens).

Anal. Calcd for $C_{19}H_{28}O_3$: C, 74.96; H, 9.27. Found: C, 74.81; H, 9.21.

8,8(7H)-Ethylenedioxy-3α,10aβ-dimethyl-3β-vinyl-2,3,5,6,6aα,9,10,10a-octahydro-1H-naptho[2,1-b]pyran (H-7)

To a solution of 2.17 g (6.45 mmoles) of ester J-1 in 400 ml of dry ether at -78° was added dropwise 24.0 ml (19.4 mmoles) of 0.81M diisibutylaluminum hydride in benzene. After 30 minutes at -78°, the reaction was quenched with 4.6 ml of absolute methanol, the dry ice-acetone bath removed, and the solution allowed to warm to room temperature; 400 ml of bicarb was added and the layers separated. The aqueous layer was extracted three times with 300 ml portions of ether, and the combined organic layers washed with 500 ml of bicarb and then 500 ml of brine. The organic layers were dried over anhydrous potassium carbonate and the solvents removed *in vacuo* to give 2.0 g (100%) of a clear, colorless viscous liquid: ir ($CHCl_3$) 1736 (C=O) and 1676 cm^{-1} (C=C); nmr ($CDCl_3$) δ 0.88 (s, 3, C-10a CH_3), 1.21 (s, 3, C-3 CH_3), 3.90 (s, 4, ketal), 9.60 (s, 1, CHO). J-3 was used in the next step without further purification.

To a solution of 1.08 g (25.7 mmoles) of 57% sodium hydride in mineral oil (washed twice with pentane) and 9.20 g (25.7 mmoles) methyltriphenylphoshonium bromide (dried in vacuum over phosphorus pentoxide) in 175 ml of dry dimethyl sulfoxide (distilled over calcium hydride) which had been stirred for one hour at room temperature, was added 1.83 g (5.98 mmoles) of crude aldehyde J-3. After 26 hours at room temperature, the solution was added to 250 ml of ether and 750 ml of water. The organic layer was separated and the aqueous layer extracted three times with 250 ml portions of ether. The combined organic layers were washed with 250 ml of water and then 250 ml of brine and dried over anhydrous potassium carbonate. Solvents were removed in vacuo and the resulting solid filtered through 10 g of silica gel with 100 ml of 3:1 petroleum ether:diethyl ether. Crystallization afforded 0.869 g (48%) of olefin H-7, a white solid, mp 62-66°. Chromatography on silica gel with 5:1 petroleum ether: diethyl ether afforded additional material (R_f 0.22). Total yield 1.21 g (67%): ir ($CHCl_3$) 1670 cm^{-1} (C=C); nmr ($CDCl_3$) δ 0.90 (s, 3, C-10a CH_3), 1.19 (s, 3, c-3 CH_3), 3.82 (s, 4, ketal), 5.5 (complex multiplet, 3, vinyl H).

One recrystallization from methanol gave analytically pure H-7, mp 67-68.5°.

Anal. Calcd for $C_{19}H_{28}O_3$: C, 74.96; H, 9.27. Found: C, 74.99; H, 9.19.

6',6'(5'H)-Ethylenedioxy-4,8'aβ-dimethyl-3',4',4'aα,7',8',8'a-hexahydrospiro[cyclohex-3α-ene-1,1'-napthalen]-2'(1'H)-one (37)

A base washed and oven dried tube containing 1.44 g (4.73 mmoles) of olefin 36 was sealed under vacuum and heated for one hour and five minutes at 170°. The tube was cooled and the contents filtered through 10 g of silica gel with 120 ml of ether to give (upon crystallization from ether) 1.11 g (77%) of a white solid, mp 102-104°. Chromatography of the filtrate on silica gel with 1.5:1 petroleum ether:diethyl ether afforded additional material (R_f .25). Total yield 1.26 g (88%): ir ($CHCl_3$) 1700 cm^{-1} (C=O); nmr ($CDCl_3$) δ 0.79 (s, 3, C-8'a CH_3), 3.92 (s, 4, ketal), 5.25 (s, 1, $w_{\frac{1}{2}}$= 8Hz, vinyl H).

An analytical sample of 37 was prepared by crystallization from hexane and ether, mp 117-118.4°.

Anal. Calcd for $C_{19}H_{28}O_3$: C, 74.96; H, 9.27. Found: C, 74.97; H,9.18.

6',6'(5'H)-Ethylenedioxy-4,8'aβ-dimethyl-3',4',4'aα,7',-8',8'a-hexahydrospiro[cyclohex-3β-ene-1,1'-napthalen]-2'(1'H)-one (H-6)

A base washed and oven dried tube containing 30 mg (0.098 mmol) of olefin H-7 was sealed under vacuum and heated at 200-218° for one hour. The tube was cooled

and the contents chromatographed on silica gel with 8:1 benzene:ethyl acetate to give 22.6 mg (75%) of ketone H-6 (R_f 0.20): ir ($CHCl_3$) 1705 cm^{-1} (C=O); nmr ($CDCl_3$) δ 0.71 (s, 3, C-8'a CH_3), 3.92 (s, 3, ketal), 5.40 (s, 1, $w_{\frac{1}{2}}$= 8 Hz).

An analytical sample of H-6 was prepared by crystallization from hexane and ether, mp 97-98.6°.

Anal. Calcd for $C_{19}H_{28}O_3$: C, 74.96; H, 9.27. Found: C, 75.01; H, 9.26.

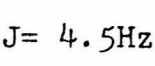
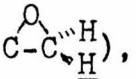
A sample of 46 mg (0.151 mmol) of olefin H-7 heated at 176-180° for two hours gave after chromatography on silica gel (8:1 benzene:ethyl acetate) 9.4 mg (20%) ketone H-6 and 32.4 mg (70%) starting material, H-7 (R_f 0.45).

6',6'(5'H)-Ethylenedioxy-4,8'aβ-dimethyl-2'α-oxaspira-3',4',4'aα,7',8',8'a-hexahydrospiro[cyclohex-3α-ene-1,1'(2'H)-napthalene] (K-3)

To a solution of 11.0 ml (25.8 mmoles) of 2.35 M n-butyllithium and 3.90 ml (3.04 g, 26.2 mmoles) of tetramethylethylenediamine (distilled over calcium hydride) at 0° was added 1.94 ml (1.64 g, 26.4 mmoles) of dimethyl sulfide (distilled over phosphorus pentoxide). After five minutes at 0°, the solution was stirred for five hours at room temperature; 1.6 ml (2.4 mmoles) of this 1.5 M $LiCH_2SCH_3$ solution was treated with a solution of 170 mg (0.56 mmoles) of ketone 37 in 4.0 ml of dry tetrahydrofuran

at -78°. After 15 minutes at -78°, the dry ice-acetone bath was removed. The solution was stirred for an additional 75 minutes, and 20 ml of water added. The solution was extracted four times with 20 ml portions of ether, and the combined organic layers washed three times with 30 ml portions of brine, dried over anhydrous potassium carbonate, and the solvents removed *in vacuo*. Chromatography on silica gel with 2:1 petroleum ether:diethyl ether afforded 43 mg (21%) starting ketone 37 (R_f 0.21) and 142 mg (69%) of alcohol K-1 (R_f 0.38) as a colorless oil: ir ($CHCl_3$) 3470 cm^{-1} (OH); nmr ($CDCl_3$) δ 1.21 (s, 3, C-8'a CH_3), 3.94 (s, 4, ketal), 5.40 (s, 1, $w_{\frac{1}{2}}$= 8 Hz, vinyl). This material was used directly without further purification.

A solution of 403 mg (1.10 mmoles) of alcohol K-1 and 30 ml (68 g, 480 mmoles) of dry methyl iodide in 15 ml of acetone (dried over anhydrous potassium carbonate) was stirred for 28 hours at room temperature. An additional 15 ml (34 g, 240 mmoles) of dry methyl iodide was added and the solution stirred for an additional 23 hours at room temperature. All solvents were then removed *in vacuo* to give 560 mg (100%) of the crude iodide salt K-2. Without further purification, 560 mg (1.10 mmoles) of K-2 in 40 ml (20 mmoles) of 0.5 M sodium hydroxide and 40 ml of methylene chloride (a two phase system) was stirred for 15 hours at room temperature before being added

to 160 ml of water and 160 ml of dichloromethane. The layers were separated and the aqueous layer extracted three times with 160 ml portions of dichloromethane. The combined organic layers were washed with 160 ml of of brine and dried over anhydrous potassium carbonate, and the solvents removed *in vacuo*. Chromatography on silica gel with 2:1 petroleum ether:diethyl ether gave 246 mg (70%) of epoxide K-3 (R_f 0.26) as a white solid, mp 50-54°: ir ($CHCl_3$) 910 cm^{-1}; nmr ($CDCl_3$) δ 1.00 (s, 3, C-8'a CH_3), 2.20 (d, 2, J= 4.5Hz, ), 2.76 (d, 2, ), 3.94 (s, 4, ketal), 5.48 (s, 1, $w_{\frac{1}{2}}$= 10Hz, vinyl).

One recrystallization from hexane gave an analytical sample of epoxide K-3, mp 50-53° (bulb-to-bulb distilled at 120° at 0.005 torr).

Anal. Calcd for $C_{20}H_{30}O_3$: C, 75.43; H, 9.50. Found: C, 75.48; H, 9.51.

Attempted Formation of Epoxide K-3 using Dimethyloxosulfonium Methylide

To a suspension of 15 mg (0.3 mmol) of 57% sodium hydride in mineral oil (washed twice with pentane) and 63 mg (0.3 mmol) of trimethyloxosulfonium iodide in 1.5 ml dry dimethyl sulfoxide (distilled over calcium hydride) which had been stirred at room temperature for 30 minutes, was added 42 mg (0.14 mmol) of ketone

37 and the resulting solution stirred for 22 hours at room temperature. The solution was then heated for 90 minutes at 50°, cooled, and added to 40 ml of water and 15 ml of ether. The layers were separated and the aqueous layer extracted three times with 15 ml portions of ether. The combined ether layers were washed with 10 ml of water and then 15 ml of brine, and dried over anhydrous sodium sulfate. Removal of solvents in vacuo gave (by nmr) only starting ketone 37.

Attempted Addition to Ketone H-6 with Lithium Dimethyl Sulfide

To a solution of 11.0 ml (25.8 mmoles) of 2.35 M n-butyllithium and 3.90 ml (3.04 g, 26.2 mmoles) of tetramethylethylenediamine (distilled over calcium hydride) at 0° was added 1.94 ml (1.64 g, 26.4 mmoles) of dimethyl sulfide (distilled over phosphorus pentoxide). After five minutes at 0°, the solution was stirred for five hours at room temperature; 0.44 ml (0.66 mmol) of this 1.5 M solution of $LiCH_2SCH_3$ was treated with 46 mg (0.15 mmol) of ketone H-6 in 5.0 ml of dry tetrahydrofuran at -98° (methanol-liquid nitrogen bath). After one hour at -98°, the bath was removed, and the solution warmed to room temperature. After three hours 20 ml of water and 20 ml of ether were added. The aqueous layer was extracted three more times with 20 ml portions of ether,

and the combined organic layers washed three times with 30 ml portions of brine and dried over anhydrous potassium carbonate. Chromatography on silica gel with 100% ether gave 40 mg (87%) of starting ketone H-6 (R_f 0.55) and 7 mg (13%) of an alcohol (R_f 0.42): ir ($CHCl_3$) 3400 cm^{-1} (OH).

Attempted Addition to Ketone H-6 with 2-Lithio-2-(trimethylsilyl)-1,3-dithiane (L-3)

To a solution of 34.6 mg (0.179 mmol) of 2-(trimethylsilyl)-1,3-dithane in 2.0 ml of dry tetrahydrofuran at -78° was added dropwise 0.08 ml (0.2 mmol) of 2.36 M n-butyllithium. After two hours at -78°, the solution was stirred for three hours at 0° and then 25 minutes at room temperature. The solution was then cooled to -78° and 54.3 mg (0.178 mmol) of ketone H-6 added. The acetone-dry ice bath was removed and after 16 hours at room temperature 30 ml of water and 30 ml of dichloromethane were added. The layers were separated and the aqueous layer extracted with an additional 30 ml of dichloromethane. The combined organic layers were washed five times with 25 ml water and once with with 25 ml of brine, and dried over anhydrous potassium carbonate. Chromatography afforded 50 mg (92%) of starting ketone H-6.

Attempted Rearrangement of Epoxide K-3 with Boron Trifluoride Etherate

To a solution of 44 mg (0.138 mmol) of epoxide K-3 in 5.0 ml dry dichloromethane at -25° was added 35 μl (40 mg, 0.28 mmol) of boron trifluoride etherate (twice distilled over calcium hydride). After 15 minutes at -25°, the reaction was quenched with 0.20 ml (o.15 g, 1.4 mmoles) of triethylamine and then 3.0 ml of bicarb. The solution was taken up in 15 ml of ether, and the organic layer washed with 5 ml water and then 5 ml brine, and dried over anhydrous potassium carbonate. Solvents were removed in vacuo and preparative tlc with 1:1 petroleum ether:diethyl ether afforded 17.6 mg (40%) of an aldehyde (R_f 0.42): nmr ($CDCl_3$) δ 0.81 (s, 3, C-8'a CH_3), 3.95 (s, 4, ketal), 5.41 (s, 1, $w_{\frac{1}{2}}$= 9Hz), 10.12 (s, 1, CHO).

Attempted Rearrangement of Epoxide K-3 with Lithium in Ethylenediamine

To a solution of 58 mg (0.182 mmol) of epoxide K-3 and 34 μl (27 mg, 0.36 mmol) of dry t-butanol in 2.0 ml of dry tetrahydrofuran and 3.0 ml dry ethylenediamine (distilled over calcium hydride) was added 45 mg (7 mmoles) of lithium, and the solution warmed to 50°. After 20 minutes the blue color disappeared so an additional 90 mg (14 mmoles) of lithium wire was

added and stirring maintained at 50° for another 45 minutes whereupon 40 ml of water and 40 ml of ether were added. The layers were separated and the aqueous layer extracted four times with 40 ml portions of ether. The combined organic layers were washed once with 40 ml of water and twice with 40 ml of brine, and dried over anhydrous potassium carbonate. Solvents were removed *in vacuo* and the residue chromatographed (ptlc) on silica gel with 9:1 ether:petroleum ether to give 29 mg of a liquid (R_f 0.36; ir ($CHCl_3$) 3600 and 3425 cm^{-1} (OH)) and 20 mg of a solid (R_f 0.55; mp 82-92°; ir ($CHCl_3$) 3600 (OH) and 1702 cm^{-1} (C=O); mass measured molecular ion calcd for $C_{18}H_{28}O_2$; 276.208919; found 276.2090 ± 0.0003).

5',5'(4'H)-Ethylenedioxy-2'-methoxycarbonyl-4,7'aβ-dimethyl-2',3',3'aα,6',7',7'a-hexahydrospiro[cyclohex-3β-ene-1,1'-indene] (M-3 and M-4)

To a solution of 177 mg (0.581 mmol) of ketone H-6 and 2.80 ml (1.23 mmoles) of 0.44 M potassium t-butoxide (in t-butanol) in 4.0 ml of dry t-butanol which had been stirred for four hours at room temperature was added 0.80 ml (70 mg, 5.95 mmoles) of isoamyl nitrite. After 19 hours at 25°C, the reaction was neutralized with 2% aqueous sulfuric acid. 25 ml water was added and the solution extracted four times with 25 ml portions of ether. The combined organic layers were washed with brine and dried

over anhydrous sodium sulfate. Solvents were removed *in vacuo* and the residue chromatographed on silica gel with 1:1 petroleum ether:diethyl ether to give 155 mg (80%) of oximo ketone M-1 (R_f 0.08) as a white solid, mp 230-233° (dec): ir ($CHCl_3$) 3550 and 3260 (OH), 1708 (C=O), 1609 cm^{-1} (C=N); nmr ($CDCl_3$) δ 0.85 (s, 3, C-8'a CH_3), 3.92 (s, 4, ketal), 5.40 (s, 1, $w_{\frac{1}{2}}$= 10Hz, vinyl).

To a solution of 149 mg (0.445 mmol) of oximo ketone M-1, 2.25 ml (9 mmoles) of 4 N aqueous sodium hydroxide, 0.75 ml (12 mmoles) of 15M ammonium hydroxide, and 23 ml of tetrahydrofuran at 10° was added 1.90 ml (1.35 mmoles) of 5.25% sodium hypochlorite (Clorox) over five minutes. The reaction was stirred for an hour at 10° and then for five hours at room temperature before the addition of 200 ml water and 200 ml of dichloromethane. The layers were separated and the aqueous layer extracted with an additional 200 ml of dichloromethane. The combined organic layers were washed once with 200 ml of brine, dried over anhydrous magnesium sulfate, and the solvents removed *in vacuo*. Chromatography on silica gel with 1:1 petroleum ether: diethyl ether afforded 144 mg (97%) of diazo ketone M-2 (R_f 0.18) as a yellow-orange solid, mp 104-108°: ir ($CHCl_3$) 2070 (N_2), 1702 (C=O), and 1620 cm^{-1} (C=N); nmr ($CDCl_3$) δ 0.91 (s, 3, C-8'a CH_3), 3.96 (s, 4, ketal), 5.40 (s, 1, $w_{\frac{1}{2}}$= 10Hz, vinyl).

A solution of 81 mg (0.245 mmol) of diazo ketone M-2 and 177 mg of sodium bicarbonate in 30 ml of dry methanol and 30 ml dry tetrahydrofuran was photolyzed for one hour at room temperature (water bath) with nitrogen bubbling through the solution and using a Hanovia medium pressure mercury vapor lamp with a quartz immersion well and a pyrex filter. Water (250 ml) was added and the solution extracted three times with 250 ml portions of dichloromethane. The combined aqueous layers were washed with 250 ml of brine, dried over anhydrous potassium carbonate, and the solvents removed *in vacuo*. Chromatography on silica gel with 3:1 petroleum ether:diethyl ether afforded 66 mg (81%) of esters M-3 and M-4. Ester M-3 (36 mg, 44%) was a yellow oil (R_f 0.17): ir ($CHCl_3$) 1720 cm^{-1} (C=O); nmr ($CDCl_3$) δ 0.82 (s, 3, C-7'a CH_3), 3.61 (s, 3, OCH_3), 3.84 (s, 4, ketal), 5.43 (s, 1, $w_{\frac{1}{2}}$= 8Hz, vinyl); mass measured molecular ion calcd for $C_{20}H_{30}O_4$: 334.214396; found: 334.2143 ± 0.0003. Ester M-4 (30 mg, 37%) was a white solid (R_f 0.25), mp 104-108°: ir ($CHCl_3$) 1718 cm^{-1} (C=O); nmr ($CDCl_3$) δ 0.91 (s, 3, C-7'a CH_3), 3.53 (s, 3, OCH_3), 3.93 (s, 4, ketal), 5.27 (s, 1, $w_{\frac{1}{2}}$= 8Hz, vinyl).

An analytical sample of ester M-4 was prepared by one recrystallization from hexane, mp 108-110°.

Anal. Calcd for $C_{20}H_{30}O_4$: C, 71.82; H, 9.04. Found: C, 71.91; H, 9.01.

1-(t-Butyldimethylsiloxy)-6,6(5H)-ethylenedioxy-8aβ-methyl-3,4,4aα,7,8,8a-hexahydronapthalene (N-1)

To 0.80 ml (0.58 g, 5.7 mmoles) of dry diisopropylamine (distilled over calcium hydride) in 10 ml of dry tetrahydrofuran at -50° was added 2.20 ml (5.1 mmoles) of 2.32M n-butyllithium in hexane. After two minutes at -50°, the cooling bath was removed. After an additional ten minutes the solution was cooled to -78° and 30 ml of dry tetrahydrofuran was added followed by 1.01 g (4.51 mmoles) of ketone I-6 (35) (using 10 ml of dry THF for the transfer). The solution was stirred for five minutes at -78° and then 5.0 ml of dry hexamethylphosphortriamide (distilled over calcium hydride) was added dropwise followed by 1.50 ml (5.06 mmoles) of 3.37M t-butyldimethylsilyl chloride in hexane (all at once). After two minutes at -78° the acetone-dry ice bath was removed and the solution stirred for one hour before addition of 500 ml of pentane. The pentane solution was washed three times with 60 ml portions of ice water and then once with 125 ml of brine, dried over anhydrous potassium carbonate, and the solvents removed *in vacuo* to give 1.60 g (105%) of crude enol ether N-1 (95% pure by vpc at 210°) which was used directly in the next step without further purification.

Analytically pure material was prepared by crystallization from hexane to give a white solid, mp 39-42°:

followed by bulb-to-bulb distillation at 145-150° (0.16 mm): ir ($CHCl_3$) 1660 cm^{-1} (C=C); nmr ($CDCl_3$) δ 0.17(s, 6, $SiCH_3$), 0.93 (s, 9, t-butylsilyl), 1.02 (s, 3, C-8a CH_3) 3.80 (s, 4, ketal), 4.60 (m, 1, vinyl).

Anal. Calcd for $C_{19}H_{34}O_3Si$: C, 67.41; H, 10.12. Found: C, 67.36; H, 10.01.

2-Chloromethylene-6,6(5H)-ethylenedioxy-8aβ-methyl-3,4,4aα,7,8,8a-hexahydro-1(2H)-napthalenone (N-5)

A solution of 111.8 mg (0.33 mmol) of silyl enol ether N-1 (crude), 0.278 g (0.63 mmol) of phenyl(bromodichloromethyl)mercury (93), and 5.0 ml of dry benzene was stirred at 80° for 15½ hours. This was cooled and decanted and the solid washed two times with 5 ml of benzene. The supernatant liquid was removed in vacuo to give an oil which was chromatographed on silica gel with 4:1 petroleum ether:diethyl ether to give 111 mg (80%) of compound N-2 (R_f 0.26). Without further purification 70 mg (0.166 mmol) of ether N-2 in 1.0 ml of dry tetrahydrofuran and 0.17 ml (0.25 mmol) of 1.44M tetrabutylammonium fluoride was stirred for one hour at room temperature; 30 ml of water was added and the solution extracted four times with 40 ml portions of ether. The combined ether layers were washed with 40 ml of brine, dried over anhydrous potassium carbonate, and the solvents removed in vacuo. Chromatography on silica gel with 2:1 petroleum ether:diethyl ether afforded 36 mg (80%) of

ketone N-5 (R_f 0.22) with a positive Beilstein test: ir ($CHCl_3$) 1685 (C=O) and 1585 cm^{-1} (C=C); nmr ($CDCl_3$) δ 1.02 (s, 3, C-8a CH_3), 3.93 (s, 4, ketal), 7.00 (m, 1, vinyl).

Crystallization from hexane and ether furnished an analytically pure sample of N-5, mp 90-92°.

Anal. Calcd for $C_{14}H_{19}ClO_3$: C, 62.11; H, 7.07; Cl, 13.09. Found: C, 62.06; H, 7.01; Cl, 12.99.

6,6(5H)-Ethylenedioxy-2α,8aβ-dimethyl-3,4,4aα,7,8,8a-hexahydro-1(2H)-napthalenone (N-6)

A. From Alkylation of Ketone I-6

To 0.16 ml (0.116 g, 1.14 mmol) of dry diisopropylamine (distilled over calcium hydride) in 2 ml of dry tetrahydrofuran at -50° was added o.44 ml (1.02 mmoles) of 2.32M n-butyllithium (in hexane). After two minutes at -50°, the cooling bath was removed. After an additional ten minutes the solution was cooled to -78°and 6 ml of dry tetrahydrofuran was added followed by 200 mg (0.90 mmol) of ketone I-6 (35), using 3 ml of dry tetrahydrofuran for the transfer. The solution was stirred for five minutes at -78°, warmed to room temperature, and 0.10 ml (0.23 g, 1.6 mmoles) of dry methyl iodide added all at once. After 25 minutes at room temperature, 100 ml of ether was added and the solution washed with 40 ml of water and then 40 ml of brine. The aqueous layers were

extracted with an additional 50 ml of ether. The combined organic layers were dried over anhydrous potassium carbonate and the solvents removed *in vacuo* to give 216 mg (101%) of the ketone mixture N-7. The crude mixture was stirred for three hours at room temperature in 25 ml absolute ethanol containing 2.5 ml of a 10% solution of potassium hydroxide in water. 100 ml ether was added and the solution washed with 50 ml water and then 50 ml brine. The aqueous layers were extracted with an additional 50 ml ether and the combined organic layers dried over anhydrous potassium carbonate. The solvents were removed *in vacuo* to give 209 mg (99%) of ketone N-6 as a white solid, mp 78-85°: ir ($CHCl_3$) 1700 cm^{-1} (C=0); nmr ($CDCl_3$) δ 1.00 (d, 3, J= 6Hz, C-2 CH_3), 1.18 (s, 3, C-8a CH_3), 3.92 (s, 4, ketal).

One recrystallization from ether furnished analytically pure material, mp 92.7-92.9°.

Anal. Calcd for $C_{14}H_{22}O_3$: C, 70.56; H, 9.30. Found: C, 70.48; H, 9.28.

B. From Hydrogenation of Compound N-5

A solution of 100 mg (0.369 mmol) of ketone N-5, 25 mg of 105 palladium on charcoal, 2.0 ml of 10% potassium hydroxide in water, and 20 ml of absolute ethanol was hydrogenated at atmospheric pressure for two hours at room temperature. The solution was filtered through celite and the residue washed with ether. Another

100 ml ether was added, the filtrate washed with 50 ml water and then 50 ml of brine. The aqueous layers were extracted with an additional 50 ml of ether and the combined organic layers dried over anhydrous potassium carbonate. Chromatography on silica gel with 2:1 petroleum ether: diethyl ether afforded 78 mg (89%) of ketone N-6 (R_f 0.25).

C. From Dissolving Metal Reduction of Compound N-5

To a solution of 29 mg (4.5 mmoles) of lithium in 2.0 ml of dry tetrahydrofuran and 18 ml of dry ammonia (distilled over lithium) was added dropwise over 30 minutes, 133 mg (0.49 mmol) of ketone N-5 and 34 mg (0.46 mmol) of dry t-butanol in 4.0 ml of dry tetrahydrofuran. After another 70 minutes the reaction was quenched with sodium benzoate (to remove the blue color) and 240 mg (4.5 mmoles) of ammonium chloride; 40 ml of water was added and the solution extracted three times with 60 ml portions of ether. The combined ether layers were washed twice with 30 ml of 15% sodium carbonate and twice with 40 ml of brine. The organic layer was dried over anhydrous potassium carbonate and the solvents removed in vacuo to give 109 mg (93%) of ketone N-6.

Attempted Ring Expansion of Ketone I-6 with Diazomethane

To a solution of 1.12 g (5.0 mmoles) of ketone I-6 and 0.5 g of potassium hydroxide in 50 ml of ether and 73 ml of absolute methanol at 0° was added 100 ml (50 mmoles) of 0.5 M diazomethane in ether. The solution was slowly allowed to warm to room temperature and after 12 hours was neutralized with 1.2 M hydrochloric acid. The solution was added to 150 ml of water and extracted three times with 200 ml portions of ether. The combined ether layers were washed with 200 ml of bicarb and then 200 ml of brine, and dried over anhydrous potassium carbonate. The solvents were removed *in vacuo* to give a yellow oil which was 97% starting ketone I-6 by vpc (at 200°).

Attempted Preparation of 2-Methyl-1,3-cycloheptanedione (51)

A. From 2-Buten-2-ol Acetate and Adipoyl Chloride

To a solution of 1.5 g (11 mmoles) of aluminum trichloride in 20 ml of distilled nitromethane at 6° was added 1.0 g (5.5 mmoles) of distilled adipoyl chloride. The reaction was warmed to room temperature and 1.2 g (11 mmoles) distilled 2-buten-2-ol acetate added. The resulting slurry was heated at 80-85° for four hours. After cooling to 0°, 3 ml of 10% HCl and then 40 ml of water were added. The solution was extracted four times with 50 ml portions of ether, and the combined organic layers washed three times with 80 ml of bicarb and then twice with 80 ml of brine.

The organic portion was dried over anhydrous magnesium sulfate and the solvents concentrated *in vacuo*. Distillation of the black liquid at 5 mm pressure gave only 200 mg (32%) of methyl acetylacetone (55) which distilled at 75-85°: ir ($CHCl_3$) 1700 cm^{-1} (C=O) and 1600 cm^{-1} (C=C); nmr ($CDCl_3$) δ 1.3 (d, 3, central methyl), 1.8 (s, 3', central methyl in enol form), 2.1 (s, 6', terminal methyls in enol form), 2.2 (s, 6, terminal methyls), 16.4 (s, 1, enol OH).

B. From Propionic Acid and Adipoyl Chloride

A suspension of 5.27 g (0.0395 mole) of anhydrous aluminum trichloride in 15 ml of distilled 1,2-dichloroethane at 10° was treated with 3.0 g (0.016 mole) of distilled adipoyl chloride. The solution was warmed to room temperature whereupon 2.5 g (0.034 mole) of distilled propionic acid was added. The solution was heated at 80-85° for three hours, then cooled and treated with 40 ml of 10% HCl at 0°. The aqueous solution was extracted four times with 70 ml of ether, and the combined organic layers washed twice with 50 ml of bicarb and twice with 100 ml of brine and dried over anhydrous sodium sulfate. Bulb-to-bulb distillation at 2mm furnished only 242 mg (11%) of a material which distilled at 80-100°.

1,3-Cycloheptanedione (O-4)

To a refluxing, stirred (high speed stirrer) solution of 1.0 g (43 mmoles) of sodium in 50 ml of dry toluene (distilled over calcium hydride) was added over 30 minutes 1.73 g (10 mmoles) of distilled adipoyl chloride and 5.6 g (43 mmoles) of dry trimethylsilyl chloride (distilled over calcium hydride) in 10 ml of dry toluene. After refluxing for 14 hours, the solution was cooled, 50 ml of ether was added, and the solution filtered under argon. The residue was washed twice with 50 ml portions of ether and the combined organic layers concentrated *in vacuo* and the resulting oil distilled at 90-105° (7 mm) to give 1.30 g (50%) of cyclohexene O-2. Without further purification, 400 mg (1.55 mmoles) of compound O-2 in 50 ml of dry ether was treated with 8.0 ml (4.5 mmoles) of 0.56M of the Simmons-Smith reagent prepared from the zinc-silver couple (52) [3.27 g (50 mmoles) of granular zinc, 25 mg of silver acetate, and 25 ml of glacial acetic acid] and 3.86 ml (50 mmoles) of diiodomethane in 45 ml of dry ether containing a few strands of silver wool (52). The solution was refluxed for three hours, cooled to 0°; 2 ml of pyridine added, and the solution filtered. The filtrate was concentrated *in vacuo* and chromatographed on silica gel with 5% ether/petroleum ether to give 340 mg (80%) of the desired cyclopropyl ether O-3: nmr ($CDCl_3$) δ 0.0 (s, 18, $SiCH_3$).

Without further purification 83 mg (0.30 mmol) of compound O-3 in 10 ml of hexane at -78° was treated with 17 μl (50 mg, 0.31 mmol) of bromine. The solution was allowed to warm to room temperature over a two hour period. The solution, which turned yellow upon addition of bromine, was again colorless by this time. 25 ml of water was added and the solution extracted three times with 30 ml portions of ether. The combined ether layers were washed with 50 ml of brine and dried over anhydrous magnesium sulfate. Solvents were concentrated *in vacuo* and the residue distilled 102-108° (6 mm) to give 38 mg (100%) of O-4 as a pale yellow liquid which rapidly turned brown on exposure to air. The compound did give a positive ferric chloride test but was not further characterized.

2-Methoxy-1,4,5,6,7,8-hexahydro-9H-benzocyclohepten-5-ol (P-2)

To a solution of 100 g (0.526 mole) of 2-methoxybenzosuberone (55) in 1150 ml of absolute ethanol, 420 ml of anhydrous ether, and three liters of dry ammonia (distilled over sodium) was added 90 g (4 moles) of sodium metal over 35 minutes so as to keep the solution a deep blue color. The ammonia was allowed to evaporate and 1600 ml of water added. The solution was extracted twice with 2 liter portions of ether and the ether layers washed separately with one liter of brine and dried over

anhydrous potassium carbonate. The solvents were removed in vacuo to give a white solid. Short path distillation in a base-washed apparatus at 80-110° (0.1 mm) gave 37 g (40%) of compound P-3 (R_f 0.7 with 4:1 petroleum ether:diethyl ether). The pot residue consisted of 53 g (52%) of alcohol P-2 (R_f 0.09 with 4:1 petroleum ether:diethyl ether) as a white solid, mp 86-88°. This material was used without further purification.

Recrystallization from ether and petroleum ether gave analytically pure P-2, mp 86-87.5°: ir ($CHCl_3$) 3590 (OH), 3430 (OH), and 1680 cm^{-1} (C=C); nmr ($CDCl_3$) δ 3.52 (s, 3, OCH_3), 4.60 (m, 1, vinyl).

Anal. Calcd for $C_{12}H_{18}O_2$: C, 74.19; H, 9.34. Found: C, 74.18; H, 9.30.

2-Methoxy-1,4,7,8-tetrahydro-9H-benzocyclohepten-5(6H)-one (P-4)

A solution of 47 g (0.24 mole) of alcohol P-2 and 8.5 g (0.415 mole) of dry aluminum isopropoxide (freshly distilled) in 220 ml of dry acetone (dried over 4A molecular sieves) and 390 ml of dry toluene (distilled over calcium hydride) was refluxed for 4½ hours, cooled, and then added to 45 ml of water and 100 ml of brine. The layers were separated and the aqueous layer was extracted twice with 125 ml portions of ether. The combined ether layers were washed twice with 75 ml portions of brine and dried

over anhydrous potassium carbonate, and the solvents removed *in vacuo*. By tlc the reaction was about 85% complete so the reagents were combined exactly as before and refluxed for an additional five hours, cooled, and worked up exactly as before to give 55 g (109%) of ketone P-4 as a colorless oil. Normally, ketone P-4 was used without further purification.

Analytically pure material was prepared by chromatography on silica gel with 4:1 petroleum ether: diethyl ether followed by bulb-to-bulb distillation at 90-93° (0.05 mm) to give P-4 as a clear, colorless liquid (oily solid below 0°): ir ($CHCl_3$) 1695 (C=O) and 1660 cm^{-1} (C=C); nmr ($CDCl_3$) δ 2.92 (m, 4, bis-allylic), 3.53 (s, 3, OCH_3), 4.7 (m, 1, vinyl).

Anal. Calcd for $C_{12}H_{16}O_2$: C, 74.97; H, 8.39. Found: C, 74.92; H, 8.34.

2-Methoxy-4a-methyl-4,4a,7,8-tetrahydro-9H-benzocyclohepten-5(6H)-one (P-5)

To 2.5 liters of dry ammonia (distilled over sodium) containing 0.25 g of ferric nitrate hydrate was added 12 g (0.306 mole) of potassium metal. After 30 minutes 51 g (0.265 mole) of ketone P-4 dissolved in 750 ml of anhydrous ether was added via addition funnel over a 30 minute period. After an additional five minutes, 50 ml (114 g, 0.80 mole) of dry methyl iodide was added over a

two-minute period. After another fifteen minutes the ammonia was allowed to evaporate and 500 ml of water was added. The layers were separated and the aqueous layer extracted twice with 500 ml portions of ether; the combined organic layers were washed twice with 200 ml portions of brine and dried over anhydrous potassium carbonate. The solvents were removed in vacuo to give 54 g (100%) of ketone P-5 which was used in the next step without further purification.

Analytically pure material was prepared by chromatography on silica gel with 9:1 petroleum ether:diethyl ether to give P-5 (R_f 0.4) as a white solid (mp 50-52°) which was distilled at 90-95° (0.05 mm): ir ($CHCl_3$) 1690 (C=O) and 1660 cm^{-1} (C=C); nmr ($CDCl_3$) δ 1.18 (s, 3, C-4a CH_3), 3.57 (s, 3, OCH_3), 4.2 (m, 1, vinyl), 5.6 (m, 1, vinyl).

Anal. Calcd for $C_{13}H_{18}O_2$: C, 75.69; H, 8.80. Found: C, 75.51; H, 8.79.

4a-Methyl-4,4a,7,8-tetrahydro-9H-benzocycloheptene-2(3H),5(6H)-dione (Homo-Wieland-Miescher Ketone, 50)

A solution of 5.4 g (26 mmoles) of ketone P-5 and 2.4 ml 4% hydrochloric acid in 100 ml of acetone was refluxed for two hours, cooled, and added to 400 ml of water and 400 ml of ether. The layers were separated and the aqueous layer extracted twice more with 400 ml portions of ether. The combined organic layers were

washed twice with 200 ml portions of brine and dried over anhydrous magnesium sulfate, and the solvents removed *in vacuo*. Crystallization from ether afforded 2.3 g (46%) of compound **50** as a white solid. Chromatography on silica gel with 2:1 petroleum ether:diethyl ether furnished additional material (R_f 0.25) to give a total yield of 3.5 g (70%) of ketone **50**, mp 70-72° (lit. 71.5-72°) (45): ir ($CHCl_3$) 1704 (C=O), 1665 (unsat. C=O), and 1618 cm^{-1} (C=C); nmr ($CDCl_3$) δ 1.38 (s, 3, C-4a CH_3), 5.99 (s, 1, vinyl).

2-Methoxy-4aβ,5α-dimethyl-4,4a,5,6,7,8-hexahydro-9H-benzocyclohepten-5β-ol (Q-1)

To 360 ml (0.66 mole) of 1.8M methyllithium in 500 ml of anhydrous ether at 0-5° was added 53 g (0.26 mole) of ketone P-5 in 500 ml of anhydrous ether over a two hour period. After another two hours at room temperature the reaction was carefully quenched with 50 ml of water. Another 800 ml of water was added, the layers separated, and the aqueous layer extracted twice more with 800 ml portions of ether. The combined organic layers were washed twice with 400 ml portions of brine and dried over anhydrous potassium carbonate. The solvents were removed *in vacuo* to give 58 g (100%) of alcohol Q-1 which was used without further purification in subsequent steps.

Chromatography on silica gel with 2:1 petroleum ether:diethyl ether followed by bulb-to-bulb distillation at 95-100° (0.05 mm) furnished an analytically pure sample of alcohol Q-1 (R_f 0.39): ir ($CHCl_3$) 3600 (OH), 1663 and 1659 cm^{-1} (C=C); nmr ($CDCl_3$) δ 1.16 (s, 3, C-4a CH_3), 1.29 (s, 3, C-5 CH_3), 4.51 (s, 3, OCH_3), 4.5 (m, 1, vinyl), 5.7 (m, 1, vinyl).

Anal. Calcd for $C_{14}H_{22}O_2$: C, 75.63; H, 9.97. Found: C, 75.59; H, 10.09.

5β-Hydroxy-4aβ,5α-dimethyl-4,4a,5,6,7,8-hexahydro-9H-benzocyclohepten-2(3H)-one (Q-2)

A solution of 56 g (0.252 mole) of alcohol Q-1 and 63 g (0.50 mole) of oxalic acid dihydrate in 180 ml of water and 2.5 liters of absolute methanol was stirred for two hours at room temperature and then made basic with 53 g (0.50 mole) of sodium carbonate. Most of the methanol was removed in vacuo and 500 ml of water and one liter of ether added. The layers were separated and the aqueous layer extracted twice with 500 ml portions of ether. The combined organic layers were washed twice with 250 ml portions of brine and dried over anhydrous potassium carbonate. The solvents were removed in vacuo to give 47 g (90%) of ketone Q-2 (R_f 0.36 with 100% ether) which was used in subsequent steps without further purification (one compound by tlc, and vpc at 200°).

One recrystallization of the yellow-white solid from ether and petroleum ether furnished an analytically pure sample of Q-2 as white crystals, mp 139-140.2°; ir ($CHCl_3$) 3600 (OH), 1650 (C=O), and 1599 cm^{-1} (C=C); nmr ($CDCl_3$) δ 1.23 (s, 3, C-4a CH_3), 1.42 (s, 3, C-5 CH_3), 5.79 (s, 1, $w_{\frac{1}{2}}$ 2Hz, vinyl).

Anal. Calcd for $C_{13}H_{20}O_2$: C, 74.96; H, 9.68. Found: C, 75.02; H, 9.67.

5β-Hydroxy-4aβ,5α-dimethyl-3,4,4a,5,6,7,8,9aβ-octahydro-9H-benzocyclohepten-2(1H)-one (Q-4)

To a solution of 7.6 g (1.1 moles) of lithium wire in 500 ml of anhydrous ether and 4.5 liters of dry ammonia (distilled over sodium) was added 44.3 g (0.213 mole) of ketone Q-2 in 500 ml of anhydrous ether via addition funnel over a one hour period. After an additional 20 minutes, anhydrous sodium benzoate was added until the color changed from blue to yellow. 60 g (1.1 moles) of ammonium chloride was then added and the ammonia allowed to evaporate. One liter of water and two liters of ether were added, the layers separated, and the aqueous layer extracted with an additional liter of ether. The combined ether layers were washed twice with 400 ml of bicarb and then twice with 400 ml of brine. All aqueous layers were extracted with an additional liter of ether. The organic layers were dried over anhydrous potassium carbonate, and the solvents removed

in vacuo. Short path distillation at 140-144° (0.05 mm) afforded 38 g (85%) of ketone Q-4 (98% pure by vpc at 200°). This material was used without further purification.

Chromatography on silica gel with 100% ether followed by crystallization from ether and petroleum ether gave an analytically pure sample of Q-4 (R_f 0.35) as a white solid, mp 74-75.5°: ir ($CHCl_3$) 3600 (OH) and 1700 cm^{-1} (C=O); nmr ($CDCl_3$) δ 1.24 (s, 3, CH_3), 1.26 (s, 3, CH_3).

Anal. Calcd for $C_{13}H_{22}O_2$: C, 74.24; H, 10.54. Found: C, 74.22; H, 10.51.

4aβ-Methyl-5-methylene-3,4,4a,5,6,7,8,9aβ-octahydro-9H-benzocyclohepten-2(1H)-one (Q-6)

To a solution of 78 mg (0.37 mmol) of alcohol Q-4 in 5.0 ml of dry pyridine at -15° was added 0.08 ml (130 mg, 1.1 mmoles) of thionyl chloride. After 15 minutes at -15° to -10°, the solution was poured onto 25 ml ice and 25 ml water added. The solution was extracted twice with 50 ml portions of ether. The ether layers were washed separately with 50 ml of bicarb, 50 ml of water, and 50 ml of brine, and dried over anhydrous magnesium sulfate. The solvents were removed in vacuo (using a cyclohexane azeotrope to remove the pyridine) to give 47 mg (66%) of exocyclic olefin Q-6, 99% pure by vpc (at 200°) and tlc (R_f 0.29 with 7:3 petroleum ether:diethyl ether).

Analytically pure material was prepared by chromatography on silica gel with 7:3 petroleum ether:diethyl ether (to give an oily white solid which melted between 0° and 25°) followed by bulb-to-bulb distillation at 80-85° (0.05 mm) to give Q-6 as a clear, colorless liquid: ir ($CHCl_3$) 1702 (C=O) and 1623 cm^{-1} (C=C); nmr ($CDCl_3$) δ 1.30 (s, 3, C-4a CH_3), 4.84 (s, 2, vinyl).

Anal. Calcd for $C_{13}H_{20}O$: C, 81.20; H, 10.48. Found: C, 81.18; H, 10.62.

4aβ,5-Dimethyl-3,4,4a,7,8,9aβ-hexahydro-9H-benzocycloheptene-2(1H)-one (Q-5)

To 36 g (0.171 mole) of alcohol Q-4 at 130-140° was added 450 mg of resublimed iodine in 75 mg batches every 10 minutes. After one hour the reaction was cooled, 500 ml of ether added, and the solution washed, twice with 250 ml portions of 10% sodium thiosulfate, once with bicarb, and once with brine. The aqueous layers were extracted with an additional 300 ml of ether, and the combined ether layers dried over anhydrous magnesium sulfate. The solvents were removed in vacuo to give 33 g (100%) of a 57:43 ratio (by vpc at 190°, Q-6 eluted first) of Q-6:Q-5. This mixture was not normally further purified but used directly in the ketalization.

To obtain pure endocyclic olefin Q-5, 964 mg of this mixture was chromatographed on silica gel with 7:3 petroleum ether:diethyl ether to give 203 mg (21%)

of Q-5 (R_f 0.33) and 308 mg (32%) of Q-6 (R_f 0.29). An analytically pure sample of Q-5 was then prepared by bulb-to-bulb distillation at 75-80° (0.05 mm) to give a clear colorless liquid: ir ($CHCl_3$) 1700 cm^{-1} (C=O); nmr ($CDCl_3$) δ 1.19 (s, 3, C-4a CH_3), 5.8 (m,1, vinyl).

Anal. Calcd for $C_{13}H_{20}O$: C, 81.20; H, 10.48. Found: C, 81.26; H, 10.49.

2,2(1H)-Ethylenedioxy-4aβ,5-dimethyl-3,4,4a,7,8, 9aα-hexahydro-9H-benzocycloheptene (Q-8)

A solution of 149 mg (0.776 mmol) of chromatographed Q-5, 3.1 mg of para-toluenesulfonic acid monohydrate, 0.28 ml (310 mg, 5.0 mmoles) of ethylene glycol, and 10 ml of dry benzene was refluxed for three hours using a Dean-Stark trap to remove the water formed. Ether (50 ml) was added and the solution washed twice with 50 ml portions of bicarb and twice with 50 ml portions of brine. The aqueous layers were extracted with an additional 100 ml of ether and the combined organic layers dried over anhydrous potassium carbonate. The solvents were removed in vacuo to give 183 mg (100%) of ketal Q-8 which was normally used without further purification.

Analytically pure material could be prepared by chromatography on silica gel with 9:1 petroleum ether: diethyl ether followed by bulb to bulb distillation at 85-90° (0.05 mm) to give Q-8 (R_f 0.25) as a clear, colorless

liquid: nmr ($CDCl_3$) δ 1.09 (s, 3, C-4a CH_3), 3.90 (s, 4, ketal), 5.47 (m, 1, vinyl).

Anal. Calcd for $C_{15}H_{24}O_2$: C, 76.23; H, 10.24. Found: C, 76.21; H, 10.29.

2,2(1H)-Ethylenedioxy-4aβ-methyl-5-methylene-3,4,4a,5,6,7,8,9aβ-octahydro-9H-benzocycloheptene (Q-9)

Identical conditions as used to produce ketal Q-8 from ketone Q-5 were used to produce ketal Q-9 from ketone Q-6. Chromatography on silica gel with 9:1 petroleum ether:diethyl ether followed by bulb-to-bulb distillation at 100-110° (0.05 mm) gave ketal Q-9 (R_f 0.3) as a clear, colorless liquid: ir ($CHCl_3$) 1628 cm^{-1} (C=C); nmr ($CDCl_3$) δ 1.12 (s, 3, C-4a CH_3), 3.68 (s, 4, ketal), 4.75 (s, 2, vinyl).

Anal. Calcd for $C_{15}H_{24}O_2$: C, 76.23; H, 10.24. Found: C, 76.13; H, 10.26.

Attempted Equilibration of Compound Q-9 with Tris-(triphenyphosphine)chlororhodium

A solution of 140 mg (0.59 mmol) of exocyclic olefin Q-9, 0.37 g (0.40 mmol) of tris-(triphenylphosphine)-chlororhodium, 13 mg (0.12 mmol) of diazobicyclo[2.2.2]-octane, and 20 ml of 95% ethanol was refluxed for 30 minutes, cooled, and added to 50 ml of water. The solution was extracted three times with 50 ml portions of ether, and

the combined organic layers washed with 50 ml of bicarb and then 50 ml of brine, and then dried over anhydrous potassium carbonate. The solvents were removed *in vacuo* to give a material which was still 100% exocyclic olefin by vpc (at 180°).

Attempted Oxidation of Compound Q-9 with Selenium Dioxide

A solution of 30 mg (0.127 mmol) of exocyclic olefin Q-9 and 7 mg (0.063 mmol) of selenium dioxide in 6.0 ml of 95% ethanol was refluxed for one hour, cooled, and added to 50 ml of bicarb. The solution was extracted with 100 ml of ether, and the ether layer washed with 50 ml of brine and dried over anhydrous potassium carbonate. The solvents were removed *in vacuo* to give 25 mg (100%) of exocyclic olefin Q-6 , 95% pure by vpc (at 190°), nmr and tlc.

2,2(1H)-Ethylenedioxy-4aβ-methyl-5-methylene-3,4,4a, 7,8,9aβ-hexahydro-9H-benzocyclohepten-6(5H)-one (Q-10)

A solution of 183 mg (0.775 mmol) of endocyclic olefin Q-8 (90% pure by vpc at 180°), 3.1 mg of hematoporphyrin dihydrochloride, 7.5 ml of pyridine, and 8.5 ml of ethyl acetate was irradiated for two hours with a 450-W Hanovia medium-pressure mercury vapor lamp in a pyrex jacket cooled to 10° with oxygen being bubbled through the solution. The solution was added to 5.5 ml of acetic

anhydride and stirred for two hours at room temperature before being carefully added to 50 ml of cold 15% sodium carbonate. The solution was extracted three times with 50 ml portions of ether, and the combined ether layers washed three times with 50 ml portions of bicarb and dried over anhydrous potassium carbonate. The solvents were removed *in vacuo* and the residue chromatographed on Florisil with 1:1 petroleum ether:diethyl ether to give 161 mg (83%) of ketone Q-10 (R_f 0.21) as a clear colorless liquid (which was a white solid at -78°).

Analytically pure material was available from distillation at 110-120° (0.05 mm): ir ($CHCl_3$) 1675 (C=O) and 1595 cm^{-1} (C=C); nmr ($CDCl_3$) δ 1.22 (s, 3, C-4a CH_3), 3.82 (s, 4, ketal), 5.23 (s, 1, vinyl), 5.65 (s, 1, vinyl).

Anal. Calcd for $C_{15}H_{22}O_3$: C, 71.97; H, 8.86. Found: C, 71.96; H, 8.80.

Preparation of Ketal Mixture Q-8 and Q-9 from Olefin Mixture Q-5 and Q-6

A solution of 33 g (0.17 mole) of a crude mixture of Q-5 and Q-6 (43% endocyclic olefin and 57% exocyclic olefin by vpc at 190°), 0.6 g (3 mmoles) of *para*-toluenesulfonic acid monohydrate, 60 ml of ethylene glycol, and 600 ml of benzene was refluxed for 3.5 hours using a Dean-Stark trap to remove the water that was

formed. After the 3.5 hours, 3.0 ml of water had separated out, so the reaction was cooled and washed twice with 300 ml portions of bicarb and twice with 250 ml portions of brine. The aqueous layers were extracted with an additional 400 ml of ether, and the combined organic layers dried over anhydrous potassium carbonate. The solvents were removed *in vacuo*, and the residue short path distilled in a base washed apparatus at 100-110° (0.05 mm) to give 34 g (85%) of a mixture of ketals Q-8 and Q-9 (43% endocyclic olefin Q-8 and 57% exocyclic olefin Q-9 by vpc at 80°).

Preparation of Methylene Ketone Q-10 from Olefin Mixture of Q-8 and Q-9

A solution of 1.06 g (4.49 mmoles) of a mixture of endocyclic olefin Q-8 (43%) and exocyclic olefin Q-9 (57%), 20 mg of hematoporphyrin dihydrochloride, 9.0 ml of pyridine, and 10 ml of ethyl acetate was irradiated with a Hanovia 450-W medium-pressure mercury vapor lamp in a pyrex jacket cooled to ~10° while oxygen was bubbled continously through the solution. After one hour 45 ml of oxygen had been absorbed (45% of theoretical) so the solution was added to 7.0 ml of acetic anhydride and stirred for two hours at room temperature. The solution was then added carefully to 50 ml of cold 15% sodium carbonate and extracted three times with 50 ml

portions of ether. The combined ether extracts were washed three times with 50 ml portions of bicarb and dried over anhydrous potassium carbonate. The solvents were removed *in vacuo*, using a cyclohexane azeotrope to remove the pyridine. Chromotography on Florisil with 1:1 petroleum ether:diethyl ether afforded 550 mg (49%) of exocyclic olefin Q-9 (eluted with the second column volume of solvent and 95% pure by vpc at 180°) and 392 mg (35%) of methylene ketone Q-10 (eluted beginning with the fourth column volume of solvent and 96% pure by tlc).

Equilibration of Exocyclic Olefin Q-9 with Iodine

To 21.5 g (91.1 mmoles) of exocyclic olefin Q-9 at 135-140° was added 240 mg of resublimed iodine in batches of 40 mg every 10 minutes. After one hour the reaction was cooled and 400 ml ether added. The solution was washed twice with 200 ml portions of 10% sodium thiosulfate, once with 250 ml of bicarb, and once with 250 ml of brine. The aqueous extracts were extracted with an additional 300 ml of ether, and the combined ether extracts were dried over anhydrous potassium carbonate. The solvents were removed *in vacuo* to give 20.8 g (97%) of a black liquid which, by vpc (at 190°) was 45% endocyclic olefin Q-8 and 55% exocyclic olefin Q-9 (eluted first), and was used without further purification.

9,9(8H)-Ethylenedioxy-3β-methoxycarbonyl-3α,11aβ-dimethyl-1,2,3,5,6,7,7aβ,10,11,11a-decahydrobenzo[3,4]cyclohepta-[1,2-b]pyran (R-1) and 9,9(8H)-Ethylenedioxy-3α-methoxy-carbonyl-3β,11aβ-dimethyl-1,2,3,5,6,7,7aβ,10,11,11a-decahydrobenzo[3,4]cyclohepta[1,2-b]pyran (R-2)

A solution of 3.02 g (12.1 mmoles) of the methylene ketone Q-10 in 11 ml (10 g, 100 mmoles) of methyl methacrylate (freshly distilled over calcium hydride and stabilized with 0.5% hydroquinone) in a base washed and oven dried tube was degassed and sealed under vacuum. After heating for 25 hours at 170°, the tube was cooled and its contents (a viscous yellow oil) dissolved in 50 ml of chloroform. Then 500 ml of ether was added causing much white polymer to precipitate out of solution. The solution and precipitate were heated on a steam bath for ten minutes, filtered, and the precipitate washed twice with 200 ml portions of hot ether. Solvents were removed *in vacuo*, and the residue was filtered through 200 g of silica gel with one liter of ether. Chromatography on silica gel with 2:1 petroleum ether:diethyl ether afforded 3.40 g (80%) of a 1:1 mixture (by vpc at 250°) of esters R-1 and R-2.

The esters could be separated by medium pressure liquid chromatography with 2:1 petroleum ether:diethyl ether in nearly quantitative yield but there were always mixed fractions. For example, 1.21 g of a 3:2 mixture

of R-2 to R-3 gave 436 mg (36%) of ester R-1 (R_f 0.25) as a clear colorless liquid (solid at -78°), 70 mg (6%) of mixed fractions, and 630 mg (52%) of ester R-2 (R_f 0.20) as a white solid, mp 65-67°.

An analytically pure sample of R-1 could be prepared by bulb-to-bulb distillation at 135-140° (0.01 mm): ir ($CHCl_3$) 1730 (C=O) and 1642 cm^{-1} (C=C); nmr ($CDCl_3$) δ 1.02 (s, 3, C-11a CH_3), 1.41 (s, 3, C-3 CH_3), 3.70 (s, 3, OCH_3), 3.92 (s, 4, ketal).

Anal. Calcd for $C_{20}H_{30}O_5$: C, 68.55; H, 8.63. Found: C, 68.56; H, 8.79.

One recrystallization from hexane and ether gave an analytically pure sample of R-2 as a white solid, mp 67-69°: ir ($CHCl_3$) 1725 (C=O) and 1649 cm^{-1} (C=C); nmr ($CDCl_3$) δ 1.09 (s, 3, C-11a CH_3), 1.48 (s, 3, C-3 CH_3), 3.78 (s, 3, OCH_3), 3.92 (s, 4, ketal).

Anal. Calcd for $C_{20}H_{30}O_5$: C, 68.55; H, 8.63. Found: C, 68.56; H, 8.67.

A sample of 623 mg (2.49 mmoles) of methylene ketone Q-10 and 3.0 ml (27 mmoles) of methyl methacrylate heated for 25 hours at 154-160° gave 750 mg (86%) of a 2:1 mixture (by vpc at 250°) of R-1:R-2.

A sample of 167 mg (0.67 mmol) of methylene ketone Q-10 and 1.4 ml (13 mmoles) of methyl methacrylate heated 13.5 hours at 220-225° gave 200 mg (85%) of a 2:1 mixture (by vpc at 260°) of R-2:R-1.

9,9(8H)-Ethylenedioxy-3α,11aβ-dimethyl-1,2,3,5,6,7,7aβ,10,11,11a-decahydrobenzo[3,4]cyclohepta[1,2-b]pyran-3β-carbaldehyde (R-3)

To a solution of 7.4 g (21 mmoles) of ester R-1 in 500 ml of dry ether at -78° was added dropwise 65 ml (63 mmoles) 0.98M diisobutylaluminum hydride in hexane. The solution was stirred for 35 minutes at -78°, then 26 ml of absolute methanol was added, the acetone-dry ice bath removed and the solution allowed to warm to room temperature. After one hour one liter of bicarb was added and the solution extracted three times with one liter portions of ether. The combined ether extracts were washed with one liter of bicarb and then one liter of brine, and dried over anhydrous potassium carbonate. The solvents were removed in vacuo to give 6.7 g (100%) of aldehyde R-3 as a pale yellow oil which was used without any further purification.

A sample of R-3 was distilled twice at 138-140° (0.005 mm) to give an analytically pure pale yellow liquid (solid at -78°): ir ($CHCl_3$) 1735 (C=O) and 1638 cm^{-1} (C=C); nmr ($CDCl_3$) δ 1.07 (s, 3, C-11a CH_3), 1.21 (s, 3, C-3 CH_3), 3.97 (s, 4, ketal), 9.53 (s, 1, CHO).

Anal. Calcd for $C_{19}H_{28}O_4$: C, 71.22; H, 8.81. Found: C, 71.29; H, 8.94.

9,9(8H)-Ethylenedioxy-3β,11aβ-dimethyl-1,2,3,5,6,7,7aβ,10,11,11a-decahydrobenzo[3,4]cyclohepta[1,2-b]pyran-3α-carbaldehyde (R-4)

In a completely analogous manner as the formation of R-3 from R-1, 5.7 g (16 mmoles) of ester R-2 in 500 ml of ether was treated with 50 ml (50 mmoles) of 0.98M diisobutylaluminum hydride in hexane, the reaction quenched with 20 ml of absolute methanol and the reaction worked up to give 5.1 g (100%) of aldehyde R-4 as a white solid (mp 120-125°) which was used without any further purification.

One recrystallization from hexane and ether gave an analytically pure sample of R-4, mp 133-135°: ir ($CHCl_3$) 1735 (C=O) and 1640 cm^{-1} (C=C); nmr ($CDCl_3$) δ 1.10 (s, 3, C-11a CH_3), 1.24 (s, 3, C-3 CH_3), 3.81 (s, 4, ketal), 9.53 (s, 1, CHO).

Anal. Calcd for $C_{19}H_{28}O_4$: C, 71.22; H, 8.81. Found: C, 71.18; H, 8.79.

Preparation of Aldehyde Mixture R-3 and R-4 from Ester Mixture R-1 and R-2

In a completely analogous manner to the formation of aldehyde R-3, 11.6 g (33 mmoles) of a 1:1 mixture of esters R-1 and R-2 in 500 ml of dry ether at -78° was treated with 100 ml (100 mmoles) of 1M diisobutylaluminum hydride in hexane, the reaction quenched with 40 ml of

absolute methanol and worked up to give 10.6 g (100%) of a 1:1 mixture (by vpc at 250°) of aldehydes R-3 and R-4 which was used without any further purification.

9,9(8H)-Ethylenedioxy-3α,11aβ-dimethyl-3β-vinyl-1,2,3,5,6,7,7aβ,10,11,11a-decahydrobenzo[3,4]cyclohepta-[1,2-b]pyran (R-5)

To a solution of 3.5 g (84 mmoles) of 57% sodium hydride in mineral oil (washed twice with pentane), 30 g (84 mmoles) of methyltriphenylphosphonium bromide (dried in a vacuum over phosphorus pentoxide), and 300 ml of dry dimethyl sulfoxide (distilled over calcium hydride) which had been stirred for one hour at room temperature, was added 6.65 g (21 mmoles) of aldehyde R-3 using 300 ml of dry dimethyl sulfoxide for the transfer. The solution was stirred for 24 hours at room temperature, added to two liters of ice water, and extracted three times with 600 ml portions of ether. The combined ether extracts were washed with 500 ml of water and then 500 ml of brine and dried over anhydrous potassium carbonate. The solvents were removed *in vacuo* and the residue filtered through 100 g of silica gel with 500 ml of 2:1 petroleum ether: diethyl ether to remove the triphenylphosphite. Crystallization from ether and petroleum ether afforded 4.3 g (65%) of compound R-5 as a white solid, mp 46-48°.

A total yield of crystalline R-5 of 5.6 g (85%) was available by chromatography of the filtrate on silica gel with 5:1 petroleum ether:diethyl ether.

One recrystallization from hexane and ether furnished an analytically pure sample of R-5, mp 47-48.5°: ir ($CHCl_3$) 1640 cm^{-1} (C=C); nmr ($CDCl_3$) δ 1.06 (s, 3, C-11a CH_3), 1.21 (s, 3, C-3 CH_3), 3.90 (s, 4, ketal), 5.42 (m, 3, vinyl).

Anal. Calcd for $C_{20}H_{36}O_3$: C, 75.43; H, 9.50. Found: C, 75.43; H, 9.43.

9,9(8H)-Ethylenedioxy-3β,11aβ-dimethyl-3α-vinyl-1,2,3,5,6,7,7aβ,10,11,11a-decahydrobenzo[3,4]cyclohepta-[1,2-b]pyran (R-6)

In a completely analogous manner as the formation of R-5 from R-3, 5.1 g (16 mmoles) of aldehyde R-4 was treated with the ylide formed from 2.7 g (64 mmoles) of 57% sodium hydride and 23 g (64 mmoles) of methyltriphenylphosphonium bromide in 600 ml of dry dimethyl sulfoxide to give, after crystallization and chromatography, 4.6 g (91%) of compound R-6 as a white solid, mp 76-79°.

One recrystallization from hexane and ether furnished an analytically pure sample of R-6, mp 80.5-82°: ir ($CHCl_3$) 1640 cm^{-1} (C=C); nmr ($CDCl_3$) δ 1.09 (s, 3, C-11a CH_3), 1.23 (s, 3, C-3 CH_3), 3.86 (s, 4, ketal), 5.39 (m, 3, vinyl).

Anal. Calcd for $C_{20}H_{30}O_3$: C, 75.43; H, 9.50. Found: C, 75.48; H, 9.53.

Preparation of R-5 and R-6 Mixture from R-3 and R-4 Aldehyde Mixture

In a completely analogous manner as the formation of R-5 from R-3, 10.5 g (33 mmoles) of a 1:1 mixture of aldehydes R-3 and R-4 was treated with the ylide formed from 5.6 g (140 mmoles) of 57% sodium hydride and 48 g (140 mmoles) of methyltriphenylphosphonium bromide in 600 ml of dry dimethyl sulfoxide to give, after chromatography, 8.45 g (81%) of a 1:1 mixture (by vpc at 240°) of R-5 and R-6 which was used without further purification.

2,2(1H)-Ethylenedioxy-4',4aβ-dimethyl-3,4,4a,8,9,9aβ-hexahydrospiro[5H-benzocycloheptene-5,1'-cyclohex-3β-en]-6(7H)-one (R-7)

A base washed and oven dried tube containing 5.1 g (16 mmoles) of olefin R-5 was sealed under vacuum and heated at 225-234°. After one hour the tube was cooled, and its contents removed and crystallized from ether to give 5.0 g (98%) of ketone R-7 (R_f 0.24 with 2:1 petroleum ether:diethyl ether) as a white solid, mp 220-226°.

One recrystallization from hexane and ether furnished an analytically pure sample of R-7, mp 131-133°: ir ($CHCl_3$) 1683 cm^{-1} (C=O); nmr ($CDCl_3$) δ 1.10 (s, 3, C-4a CH_3),

3.87 (d, 4, J= 1Hz, ketal), 5.4 (m, 1, vinyl); carbon-13 nmr ($CDCl_3$) 58.0 and 58.5 (ketal), 102.9 (C-2), 114.7 (C-3'), 128.9 (C-4'), and 209.1 ppm (C-6).

Anal. Calcd for $C_{20}H_{30}O_3$: C, 75.43; H, 9.50. Found: C, 75.41; H, 9.45.

A sample of ketone R-7 was submitted for X-ray analysis to Professor Jon Bordner of North Carolina State University.

2,2(1H)-Ethylenedioxy-4',4aβ-dimethyl-3,4,4a,8,9,9aβ-hexahydrospiro[5H-benzocycloheptene-5,1'-cyclohex-3α-en]-6(7H)-one (R-8)

A base washed and oven dried tube containing 75 mg (0.24 mmol) of olefin R-6 was sealed under vacuum and heated at 182-188°. After one hour the tube was cooled and its contents chromatographed on silica gel with 2:1 petroleum ether:diethyl ether to give 7 mg (9%) of starting olefin R-6 (R_f 0.43) and 56 mg (75%) of ketone R-8 (R_f 0.23).

Crystallization from hexane and ether afforded an analytically pure sample of R-8 as a white solid, mp 81.5-83.5°: ir ($CHCl_3$) 1705 cm^{-1} (C=O); nmr ($CDCl_3$) δ 0.94 (s, 3, C-4a CH_3), 3.93 (s, 4, ketal), 5.4 (m, 1, vinyl); carbon-13 nmr ($CDCl_3$) 58.6 (ketal), 103.6 (C-2), 117.2 (C-3'), 133.7 (C-4'), and 211.0 ppm (C-6).

Anal. Calcd for $C_{20}H_{30}O_3$: C, 75.43; H, 9.50. Found: C, 75.34; H, 9.42.

A sample of 60 mg (0.19 mmol) of olefin R-6 heated for one hour at 166-170° afforded 60 mg (100%) of a 2:1 mixture (by vpc at 240°, R-6 eluted first) of product R-8 to starting material R-6.

A sample of 3.3 g (10 mmoles) of olefin R-6 heated for one hour at 200-230° afforded 3.3 g (100%) of a 5:1 mixture (by vpc at 240°, R-8 eluted first) of ketone R-7 to ketone R-8.

A sample of 8 mg (0.025 mmol) of ketone R-8 heated for one hour at 225-235° afforded 8 mg (100%) of starting material R-8 (95% pure by vpc at 270°).

Preparation of Ketone R-7 from the Olefin Mixture of R-5 and R-6

A total of 7.6 g (24 mmoles) of a 1:1 mixture of olefins R-5 and R-6 was heated for one hour at 210-230° to give, after cooling and crystallization from ether and petroleum ether, 3.6 g (47%) of ketone R-7. Chromatography of the filtrate on silica gel with 2:1 petroleum ether: diethyl ether gave additional material (though of lower purity) so that the total yield of ketone R-7 was 4.5 g (59%). By vpc (at 250°) ketone R-7 was 90% pure, the other 10% consisting of ketone R-8. The chromatography also afforded 2.2 g (29%) of an oily white solid which was (by vpc at 250°) 85% ketone R-8 and 15% ketone R-7.

2,2(1H)-Ethylenedioxy-7-hydroxyimino-4',4aβ-dimethyl-3,4,4a,8,9,9aβ-hexahydrospiro[5H-benzocycloheptene-5,1'-cyclohex-3β-en]-6(7H)-one (S-1)

A. Attempted Preparation Using Potassium t-Butoxide

A solution of 95 mg (0.30 mmol) of ketone R-7, 1.6 ml (0.61 mmol) of 0.38M potassium t-butoxide in t-butanol, and 15 ml of dry t-butanol was stirred for one hour at room temperature before addition of 0.08 ml (0.6 mmol) of isoamyl nitrite (freshly distilled). After 27 hours at room temperature, the solution was neutralized with 2% sulfuric acid and added to 50 ml of water. The solution was then extracted four times with 50 ml portions of ether, and the combined ether extracts washed with 50 ml of brine and dried over anhydrous magnesium sulfate. The solvents were removed in vacuo to give 95 mg (100%) of crystalline starting ketone R-7 (100% pure by tlc).

B. Preparation Using n-Butyllithium

To a solution of 4.42 g (13.9 mmoles) of ketone R-7 in 250 ml of dry tetrahydrofuran at 0-5° was added dropwise 5.8 ml (13.9 mmoles) of 2.40M n-butyllithium in hexane. After the solution had been stirred for 10 minutes at 0°, 1.80 ml (1.62 g, 13.8 mmoles) of freshly distilled isoamyl nitrite was added, the solution stirred for an additional 10 minutes at 0°, and then the ice bath removed. After 3.5 hours at room temperature, the solution was made acidic (pH 6 using litmus paper) by the addition

of 2% sulfuric acid. The solution was then added to 800 ml of water and extracted four times with 800 ml portions of ether. The ether extracts were washed with 400 ml of brine and dried over anhydrous magnesium sulfate. The solvents were removed *in vacuo* and the residue crystallized from ether to give 2.0 g (42%) of oximo ketone S-1 as a white solid. Chromatography of the filtrate on silica gel with 1:1 petroleum ether: diethyl ether afforded 2.0 g (45%) of starting ketone R-7 (R_f 0.36) and 0.4 g (8%) of oximo ketone S-1 (R_f 0.14). Thus, the total yield of oximo ketone S-1, mp 225-230° (decomposes), was 2.4 g (50%).

One crystallization from chloroform and ether afforded an analytically pure sample of S-1 as a white solid, mp 238-240° (decomposes): ir ($CHCl_3$) 3555 and 3270 (OH) and 1688 cm^{-1} (C=O); nmr ($CDCl_3$) δ 1.05 (s, 3, C-4a CH_3), 3.86 (s, 4, ketal), 5.28 (m, 1, vinyl).

Anal. Calcd for $C_{20}H_{29}O_4N$: C, 69.14; H, 8.41; N, 4.03. Found: C, 69.19; H, 8.36; N, 4.04.

6',6'(5'H)-Ethylenedioxy-2'α-methoxycarbonyl-4,8'aβ-dimethyl-1',2',3',4',4'aβ,7',8',8'a-octahydrospiro[cyclohex-3β-ene-1,1'-napthalene] (S-6) and 6',6'(5'H)-Ethylenedioxy-2'β-methoxycarbonyl-4,8'aβ-dimethyl-1',2',3',4',4'aβ,7',8',8'a-octahydrospiro[cyclohex-3β-ene-1,1'-napthalene] (S-7)

A. Preparation of Diazo Ketone S-3

To a solution of 3.24 g (9.34 mmoles) of oximo ketone R-7, 47 ml (190 mmoles) of 4 N aqueous sodium hydroxide, 15.0 ml (225 mmoles) of 15 M aqueous ammonium hydroxide, and 400 ml of tetrahydrofuran at 10° was added 39 ml (27.5 mmoles) of 5.25% aqueous sodium hypochlorite (Clorox) over five minutes. The reaction was stirred for one hour at 10° and then for four hours at room temperature before the addition of one liter of water. The solution was extracted three times with one liter portions of ether, and the combined ether layers washed with 600 ml of brine and dried over anhydrous potassium carbonate. The solvents were removed *in vacuo* to give 3.3 g (100%) of diazo ketone S-3 as yellow foam. Diazo ketone S-3 (R_f 0.26 with 1:1 petroleum ether:diethyl ether) was used without further purification: ir ($CHCl_3$) 2070 (N_2), 1682 (C=O), and 1612 cm^{-1} (C=N).

B. Preparation of Esters S-6 and S-7

A solution of 3.30 g (9.60 mmoles) of diazo ketone S-3, 175 ml (96 mmoles) of 0.55 M sodium methoxide in methanol, and 420 ml of dry methanol at -70° to -80° (via a liquid nitrogen-methanol cooling bath) with a constant stream of argon bubbling through the solution was irradiated for one hour with a Hanovia 450-W medium-pressure mercury vapor lamp in a pyrex jacket (cooled by a stream of methanol at -78° via an acetone-dry ice bath). After one hour the

lamp was shut off, and the solution (which had gone from orange to yellow in color) was stirred for an additional hour at -75°. The cooling bath was then removed, and the solution allowed to warm to room temperature. After one hour, the solution was added to 2.25 liters of water and extracted with three 2.4 liter portions of dichloromethane. The combined organic extracts were washed with 1.2 liters of brine and dried over anhydrous magnesium sulfate. The solvents were removed in vacuo and the residue chromatographed on silica gel using 2:1 petroleum ether:diethyl ether to give 380 mg (11%) of ester S-7 (R_f 0.34) as a white solid, mp 105-108°, and 1.96 g (59%) of ester S-6 (R_f 0.29) as a white solid, mp 76-79°.

One recrystallization from hexane and ether gave an analytically pure sample of S-6, mp 88-90°: ir ($CHCl_3$) 1713 cm^{-1} (C=O); nmr ($CDCl_3$) δ 1.02 (s, 3, C-8'a CH_3), 3.63 (s, 3, OCH_3), 3.87 (t, 4, J= 3Hz, ketal), 5.25 (s, 1, $w_{\frac{1}{2}}$= 10 Hz, vinyl).

Anal. Calcd for $C_{21}H_{32}O_4$: C, 72.38; H, 9.26. Found: C, 72.34; H, 9.18.

One recrystallization of ester S-7 from hexane and ether gave an analytically pure sample, mp 110-112°: ir ($CHCl_3$) 1726 cm^{-1} (C=O); nmr ($CDCl_3$) δ 0.95 (s, 3, C-8'a CH_3), 3.58 (s, 3, OCH_3), 3.86 (t, 4, J= 2Hz, ketal), 5.37 (s, 1, $w_{\frac{1}{2}}$= 10Hz, vinyl).

Anal. Calcd for $C_{21}H_{32}O_4$: C, 72.38; H, 9.26. Found: C, 72.46; H, 9.32.

Photolysis of Diazoketone S-4 in Methanol at Room Temperature (Preparation of Cyclobutanone S-5)

A solution of 60 mg (0.17 mmol) of diazo ketone S-3, 130 mg (1.6 mmoles) of anhydrous sodium bicarbonate, 8.0 ml of dry methanol, and 8.0 ml of dry tetrahydrofuran at room temperature (via a large water bath) was irradiated using a Hanovia 450-W medium-pressure mercury vapor lamp in a pyrex jacket (cooled by a stream of cold water) while argon was continously bubbled through the solution. After one hour the solution was added to 50 ml of water and extracted three times with 50 ml portions of dichloromethane. The combined organic extracts were washed with 50 ml of brine and dried over anhydrous potassium carbonate. The solvents were removed in vacuo to give 60 mg (100%) of cyclobutanone S-5, 80% pure by vpc at 240°. The tlc showed no evidence for any ester formation.

Chromatography on silica gel with 55:45 petroleum ether:diethyl ether followed by crystallization from ether and hexane gave an analytically pure sample of ketone S-5 (R_f 0.28) as a white solid, mp 104-108°: ir ($CHCl_3$) 1755 cm^{-1} (C=O); nmr ($CDCl_3$) δ 0.95 (s, 3, CH_3), 1.04 (s, 3, CH_3), 3.92 (s, 4, ketal).

Anal. Calcd for $C_{20}H_{28}O_3$: C, 75.91; H, 8.92. Found: C, 75.94; H, 8.78.

A similar photolysis of 31 mg (0.090 mmol) of diazo ketone S-3 in 8 ml of dry methanol and 8 ml of dry tetrahydrofuran containing 65 mg of anhydrous sodium bicarbonate was done at -55° (via a liquid nitrogen-methanol cooling bath) for one hour to give, after work-up, 32 mg (100%) of the crude cyclobutanone S-5. The crude ketone was 80% pure by vpc (at 240°), and its tlc showed that less than 5% of either ester S-6 or ester S-7 had been formed.

Attempted Ester Equilibration Using Sodium Methoxide

A solution of 40 mg (0.11 mmol) of ester S-6, 4.0 ml (2.2 mmoles) of 0.55 M sodium methoxide in methanol, and 4.0 ml of dry methanol was refluxed for 45 hours, cooled, and added to 50 ml of water. The solution was then extracted four times with 50 ml portions of dichloromethane, and the combined organic extracts were washed with 50 ml of brine and dried over anhydrous potassium carbonate. The solvents were removed *in vacuo* to give 40 mg (100%) of starting ester S-6.

Similarly, a solution of 18 mg (0.052 mmol) of ester S-7 in 8.0 ml (4.4 mmol) of 0.55 M sodium methoxide in methanol was (by tlc) still at least 95% starting material S-7 after 6 days at reflux.

Attempted Ester Equilibration Using Lithium Diisopropylamide

To a cold (-78°) solution of lithium diisopropylamide prepared from 0.30 ml (0.72 mmol) of 2.40 M hexane solution of n-butyllithium and 0.10 ml (0.71 mmol) of dry diisopropylamine (distilled over calcium hydride) in 5.0 ml of dry tetrahydrofuran was added 18 mg (0.052 mmol) of ester S-7 and 0.50 ml of dry hexamethylphosphoramide (distilled over calcium hydride). The solution was allowed to warm to -30° over a fifteen minute period, and then was stirred at -20° to -10° for fifteen minutes more before adding 4 ml of water and 100 ml of pentane. The solution was then washed three times with 12 ml portions of water and once with 25 ml of brine and dried over anhydrous potassium carbonate. The solvents were removed in vacuo to give 18 mg (100%) which was (by tlc) about 75% starting ester S-7 and 25% cyclobutanone S-5.

Under identical conditions, 2.7 mg (0.01 mmol) of ester S-6 gave a crude tlc showing ~75% starting ester S-6 and 25% cyclobutanone S-5.

6',6'(5'H)-Ethylenedioxy-2'α-hydroxymethyl-4,8'aβ-dimethyl-1',2',3',4',4'aβ,7',8',8'a-octahydrospiro[cyclohex-3β-ene-1,1'-napthalene] (S-8)

A solution of 1.36 g (3.91 mmoles) of ester S-6 (~75% S-6 and 25% S-9 by carbon-13 nmr), 0.98 g (26 mmoles) of lithium aluminum hydride, 0.10 ml of dry pyridine,

and 140 ml of dry ether was refluxed for three hours, cooled to 0°, and quenched carefully with 1.0 ml of water, then 1.0 ml of 15% aqueous sodium hydroxide, and then 3.0 ml of water. The solution was then filtered through anhydrous magnesium sulfate (the residue washed with ether) and the solvents removed *in vacuo* to give 1.21 g (97%) of alcohol S-8 (contaminated with about 33% of T-1, R_f 0.35 with 100% ether) as a white solid, mp 168-172°.

Recrystallization from ether gave an analytically pure sample of alcohol S-8 (R_f 0.32 with 100% ether) as a white solid, mp 170-172° : ir ($CHCl_3$) 3601 cm^{-1} (OH); nmr ($CDCl_3$) δ 0.96 (s, 3, C-8'a CH_3), 3.72 (s, 1, $w_{\frac{1}{2}}$= 5Hz, alcohol), 3.83 (s, 4, $w_{\frac{1}{2}}$= 3Hz, ketal), 5.3 (s, 1, $w_{\frac{1}{2}}$= 10 Hz, vinyl).

Anal. Calcd for $C_{20}H_{32}O_3$: C, 74.96; H, 10.06. Found: C, 74.94; H, 10.04.

A sample of alcohol S-8 was submitted for X-ray analysis to Professor Jon Bordner of North Carolina State University.

A solution of 38 mg (0.11 mmol) of ester S-6 (90% pure), 13 mg (0.34 mmol) of lithium aluminum hydride, 1 ml of dry pyridine, and 4 ml of dry ether was refluxed for one hour, quenched with 0.02 ml water, 0.02 ml of 15% aqueous sodium hydroxide, and 0.04 ml of water, filtered through anhydrous magnesium sulfate, and the solvents removed *in vacuo* to give 35 mg (100%) of alcohol S-8 (83-86% pure by nmr and tlc).

3,3-Ethylenedioxy-15,16-didehydro-5-epi-18,19-dinor-aphidicolane (T-4) and 3,3-Ethylenedioxy-12,13-didehydro-5-epi-18,19-dinorstemodane (T-5)

A. Preparation of Brosylates T-2 and T-3

To a solution of 0.76 g (2.38 mmol) of a 67:33 mixture of alcohol S-8 to alcohol T-1 in 107 ml of dry pyridine at 0° was added all at once 1.21 g (4.73 mmoles) of para-bromobenzenesulfonic acid (freshly base washed, crystallized from ether, and dried in vacuo). The solution was stirred for five minutes at 0°, and the flask stoppered and placed in the refrigerator (lower compartment) at 5-6°. After 51.5 hours the solution was poured onto 250 ml of ice, then added to 750 ml of water, and extracted four times with 400 ml portions of ether. The combined ether extracts were washed with 400 ml of brine and dried over anhydrous potassium carbonate. The solvents were removed in vacuo (using a cyclohexane azeotrope to remove the pyridine) to give 1.23 g (96%) of the brosylate mixture T-2 and T-3 (R_f 0.33 with 1:1 petroleum ether:diethyl ether) as a white solid, mp 103-106° (decomposes): ir ($CHCl_3$) 1580 (Ar), 1358, 1256, and 1183 cm^{-1} (S=O); nmr ($CDCl_3$) δ 0.92 (s, 3, C-8'a CH_3), 3.88 (t, 4, J= 3Hz, ketal), 5.24 (s, 1, $w_{\frac{1}{2}}$= 9Hz, vinyl), 7.75 (d, 4, J= 1.5 Hz, aromatic). This mixture was used without further purification.

B. Solvolysis of the Brosylate Mixture

A solution of 1.23 g (2.28 mmoles) of the crude brosylate mixture of T-2 and T-3, 15 ml of dry pyridine, and 60 ml of dry dimethyl sulfoxide (distilled over calcium hydride) was heated for one hour at 110°, cooled and added to 400 ml of ice water. The solution was extracted three times with 400 ml portions of pentane, and the combined pentane layers washed with 200 ml of water, then 200 ml of bicarb, and then 200 ml of brine. The combined organic extracts were dried over anhydrous potassium carbonate, and the solvents removed *in vacuo* (using a cyclohexane azeotrope to remove the pyridine) to give 680 mg (99%) of a liquid mixture of olefins T-4 and T-5. This mixture could be hydrolyzed directly to ketones T-4 and T-5, or chromatographed on silica gel with 10:1 hexane:ethyl acetate to give 550 mg (80%) of a 60:40 mixture (by vpc at 255°, T-4 eluted first) of T-4:T-5 as a colorless liquid (R_f 0.26).

An analytical sample of the liquid mixture of T-4 and T-5 was prepared by distillation at 98-106° (0.005 mm): nmr ($CDCl_3$) δ 1.00 (s, 3, C-20 CH_3 in T-5), 1.03 (s, 3, C-20 CH_3 in T-4), 3.90 (s, 8, ketal), 5.0 (s, 3, $w_{\frac{1}{2}}$= 10 Hz vinyl), 4.4 (s, 1, $w_{\frac{1}{2}}$= 10 Hz, vinyl).

Anal. Calcd for $C_{20}H_{30}O_2$: C, 79.42; H, 10.00. Found: C, 79.46; H, 10.09.

A sample of 38 mg (0.11 mmol) of alcohol S-8 (83-86% pure) was treated with 55 mg (0.22 mmol) of dry p-bromobenzenesulfonic acid in 6 ml of dry pyridine at 5-6° for 46 hours to give after work-up, 60 mg (100%) of the brosylate mixture T-2 and T-3. Solvolysis of the brosylate mixture at 110° for one hour in 1.5 ml of dry pyridine and 6.0 ml of dry dimethyl sulfoxide gave, after work-up and chromatography on silica gel, 22 mg (69%) of a 75:25 mixture (by vpc at 260°) of T-4:T-5.

15,16-Didehydro-5-epi-18,19-dinoraphidicolan-3-one (T-8) and 12,13-Didehydro-5-epi-18,19-dinorstemodan-3-one (T-9)

A solution of 949 mg (3.14 mmoles) of a 1:1 crude mixture of ketals T-4 and T-5, 792 mg (6.28 mmoles) of oxalic acid dihydrate, 4.8 ml of water, and 64 ml of absolute methanol was stirred for four hours at room temperature and then was treated with 666 mg (6.28 mmoles) of anhydrous sodium carbonate, added to 400 ml of water, and extracted four times with 400 ml portions of ether. The combined organic extracts were washed with 300 ml of brine and dried over anhydrous magnesium sulfate. The solvents were removed *in vacuo* and the residue chromatographed on silica gel with 4:1 petroleum ether: diethyl ether to give 662 mg (82%) of a 1:1 mixture (by vpc at 245°, T-8 eluted first) of ketones T-8 and T-9

as a colorless liquid (R_f 0.23).

An analytically pure sample of the ketone mixture of T-8 and T-9 was prepared by bulb-to-bulb distillation at 125-135° (0.01 mm): ir ($CHCl_3$) 1704 cm^{-1} (C=O); nmr ($CDCl_3$) δ 1.02 (s, 3, C-20 CH_3 in T-8), 1.13 (s, 3, C-20 in T-9), 4.42 (s, 1, $w_{\frac{1}{2}}$= 8Hz, vinyl), 5.0 (s, 3, $w_{\frac{1}{2}}$= 9Hz, vinyl).

Anal. Calcd for $C_{18}H_{26}O$: C, 83.67; H, 10.14. Found: C, 83.51; H, 10.03.

Attempted Photochemical Equilibration of Endocyclic Olefins T-4 and T-5

A solution of 30 mg (0.1 mmol) of a 1:1 mixture of endocyclic olefins T-4 and T-5, 0.2 ml of dry p-xylene (distilled over calcium hydride), and 20 ml of dry isopropyl alcohol (distilled over calcium hydride) was photolyzed using a Hanovia 450-W medium-pressure mercury vapor lamp in a vycor sleeve and and a water cooled immersion well. The solution was stirred for 17 hours, but by vpc showed no change so 3 ml of glacial acetic acid was added and the solution photolyzed for an additional 23 hours. Analysis by vpc (at 250°) showed the same 1:1 ratio of T-4 to T-5, indicating that no reaction had taken place.

2α-Acetyl-9bα-ethanal-7,7(6H)-ethylenedioxy-9aβ-methyl-2,3,3aβ,4,5,5aβ,8,9,9a,9b-decahydro-1H-benz[e]indene (U-3)

A solution of 580 mg (1.92 mmoles) of the 60:40 mixture of ketals T-4:T-5, 5.0 ml of dry pyridine, and 5.0 ml of dry ether at 0° was treated with 0.25 g (0.98 mmol) of osmium tetroxide. After five minutes at 0° the solution was warmed to room temperature and stirred in the dark. After 23.5 hours the solution was cooled to 0° and was treated with 14 ml of pyridine and then 5 g of sodium bisulfite dissolved in 15 ml of water. After stirring for 1.5 hours at room temperature, the solution was added to 70 ml of water and extracted four times with 100 ml portions of chloroform. The combined organic extracts were washed with 150 ml of brine and dried over anhydrous potassium carbonate. The solvents were removed *in vacuo* and the residue chromatographed on silica gel with 6:1 ethyl acetate:benzene to give 247 mg (47%) of a 60:40 mixture of starting ketals (R_f 0.65) T-4:T-5 and 329 mg (51%) of a 60:40 mixture of diols (R_f 0.27) U-1:U-2 as a white foam: ir ($CHCl_3$) 3500 cm^{-1} (OH); nmr ($CDCl_3$) δ 0.98 (s, 3, C-20 CH_3), 1.20 (s, 3, C-17 CH_3), 3.90 (s, 4, ketal).

A solution of 83 mg (0.25 mmol) of a 60:40 mixture of U-1:U-2, 1.0 ml of pyridine, and 4.0 ml of absolute methanol was treated with 80 mg (0.35 mmol) of periodic acid dihydrate using 0.3 ml of water for the transfer.

After 30 minutes at room temperature, the solution was added to 10 ml bicarb and 40 ml of water and then extracted three times with 50 ml portions of chloroform. The combined organic extracts were washed with 50 ml of brine and dried over anhydrous potassium carbonate. The solvents were removed *in vacuo* and the residue chromatographed on silica gel with 3:1 benzene:ethyl acetate to give 17 mg (20%) of U-4 [R_f 0.26 and nmr ($CDCl_3$) δ 1.00 (s, 3, C-9a CH_3), 2.20 (s, 3, acetyl), 3.90 (s, 4, ketal), 9.9 (s, 1, $w_{\frac{1}{2}}$= 6Hz, CHO)] and 35 mg (42%) of U-3 as a white solid (R_f 0.31), mp 96-100°.

One recrystallization from hexane and ether gave an analytically pure sample of U-3 as a white solid, mp 123-126°: ir ($CHCl_3$) 1697 cm^{-1} (C=O); nmr ($CDCl_3$) δ 1.07 (s, 3, C-9a CH_3), 2.10 (s, 3, acetyl), 3.86 (s, 4, ketal), 9.9 (s, 1, $w_{\frac{1}{2}}$= 6 Hz, CHO).

Anal. Calcd for $C_{20}H_{30}O_4$: C, 71.82; H, 9.04; Found: C, 71.85; H, 9.06.

15,16-Didehydro-5-epi-18,19-dinoraphidicolan-1-en-3-one (V-5) and 12,13-Didehydro-5-epi-18,19-dinorstemodan-1-en-3-one (V-6)

To a solution of 45 mg (1.07 mmoles) of 57% sodium hydride (washed twice with pentane), 7μl (0.2 mmol) of dry methanol, and 3.0 ml of dry benzene which had been stirred for 25 minutes at room temperature was added

86 μl (1.06 mmol) of ethyl formate and 35 mg (0.213 mmol) of a 1:1 ketone mixture of T-8 and T-9 using 6.0 ml of dry benzene for the transfer. The solution was stirred for 20 hours at room temperature, cooled to 0°, quenched with 16 ml of water, neutralized with 2% aqueous sulfuric acid, and added to 150 ml of water. The solution was extracted four times with 150 ml portions of dichloromethane, and the combined organic extracts washed with 150 ml of brine and dried over anhydrous magnesium sulfate. The solvents were removed *in vacuo* to give 60 mg (98%) of a mixture of V-1 and V-2 which was used without further purification.

To a solution of 59 mg (0.206 mmol) of a mixture of V-1 and V-2 in 3.0 ml of freshly distilled dioxane at room temperature was added all at once 57 mg (0.251 mmol) of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone. After three minutes the solution was diluted with 10 ml of 4:1 hexane:ethylacetate and filtered through 12 g of silica gel using an additional 60 ml of 4:1 hexane:ethyl acetate. The solvents were removed *in vacuo* (using a cyclohexane azeotrope to remove the dioxane) to give 52 mg (89%) of a mixture of enones V-3 and V-4 as a yellow liquid (R_f 0.29) which was used without further purification: ir ($CHCl_3$) 1725 (CHO), 1675 (C=O), 1603 (C=C); nmr ($CDCl_3$) δ 1.27 (s, 3, CH_3), 1.33 (s, 3, CH_3), 4.44 (s, 1, $w_{\frac{1}{2}}$= 7Hz, vinyl), 5.10 (s, 1, $w_{\frac{1}{2}}$= 7Hz, vinyl),

7.50 (s, 1, C-1 H), 7.72 (s, 1, C-1 H), 10.1 (s, 2, CHO).

A solution of 50 mg (0.176 mmol) of a 1:1 mixture of enones V-3 and V-4, 162 mg (0.175 mmol) of tris-(triphenylphosphine)chlororhodium, and 6.0 ml of dry benzene was refluxed for three hours, cooled, and filtered through 20 g of silica gel using 100 ml of 4:1 hexane: ethyl acetate. The solvents were removed in vacuo and the residue chromatographed on silica gel using 6:1 hexane:ethyl acetate to give 28 mg (62%) of a 1:1 mixture (by vpc at 230°) of V-5 and V-6 as a colorless liquid (R_f 0.26): ir ($CHCl_3$) 1667 cm^{-1} (C=O); nmr ($CDCl_3$) δ 1.25 (s, 6, C-20 CH_3), 5.0 (s, 2, $w_{\frac{1}{2}}$= 16Hz, vinyl), 5.98 (d,1,J=10Hz,C-2 H in V-6),6.02 (d,1,J=10Hz,C-2 H in V-5), 6.64(d,1,J=10Hz,C-1 H in V-5),6.90(d,1,J=10Hz,C-1 H in V-6).

An analytically pure sample of the mixture was prepared by bulb-to-bulb distillation at 120-125° (0.005 mm) to give V-5 and V-6 as a clear, colorless liquid.

Anal. Calcd for $C_{18}H_{24}O$: C, 84.32; H, 9.44. Found: C, 84.17; H, 9.40.

15,16-Didehydro-5-epi-18-noraphidicolan-1-en-3-one (V-7) and 12,13-Didehydro-5-epi-18-norstemodan-1-en-3-one (V-8)

To a cold (-78°) solution of lithium diisopropyl-amide prepared from 32 μl (0.22 mmol) of dry diisopropyl-amine and 0.08 ml (0.2 mmol) of a 2.50 M hexane solution of n-butyllithium in 1.0 ml of dry tetrahydrofuran at -50°

was added 24.3 mg (0.095 mmol) of a 1:1 mixture of V-5 and V-6 using 2 ml of dry tetrahydrofuran for the transfer. The solution was stirred for five minutes at -78° and then for ten minutes at room temperature before adding 0.10 ml (1.6 mmol) of dry methyl iodide. The solution was stirred for 30 minutes at room temperature, added to 50 ml of water, and extracted three times with 50 ml portions of dichloromethane. The combined organic extracts were washed with 50 ml of brine and dried over anhydrous magnesium sulfate. The solvents were removed *in vacuo* and the residue chromatographed on silica gel with 6:1 hexane:ethyl acetate to give 26 mg (100%) of a 1:1 mixture (by vpc at 230°) of ketones V-7 and V-8 (R_f 0.43) as a white solid, mp 53-55°: ir ($CHCl_3$) 1665 cm^{-1} (C=O); nmr ($CDCl_3$) δ 1.10 (d, 3, J= 7Hz, C-19 CH_3 in V-8), 1.14 (d, 3, J= 7Hz, C-19 CH_3 in V-7), 1.23 (s, 3, C-20 CH_3 in V-8), 1.27 (s, 3, C-20 CH_3 in V-7), 5.0 (s, 2, $w_{\frac{1}{2}}$= 16 Hz, vinyl), 5.95 (d, 1, J= 10 Hz, C-2 H in V-8), 5.99 (d, 1, J= 10 Hz, C-2 H in V-7), 6.59 (d, 1, J= 10 Hz, C-1 H in V-7), 6.79 (d, 1, J= 10 Hz, C-1 H in V-8).

An analytically pure sample of the mixture V-7 and V-8 was prepared by bulb-to-bulb distillation at 120-125° (0.005 mm) to give a clear, colorless liquid.

Anal. Calcd for $C_{19}H_{26}O$: C, 84.39; H, 9.69. Found: C, 84.26; H, 9.78.

Attempted Hydroxymethylation of V-7 and V-8

A. Using Formaldehyde

To a cold (-78°) solution of lithium diisopropylamide prepared from 40 µl (0.28 mmol) of dry diisopropylamine (distilled over calcium hydride) and 0.10 ml (0.25 mmol) of a 2.50 M hexane solution of n-butyllithium in 1.0 ml of dry tetrahydrofuran was added 24 mg (0.09 mmol) of a 1:1 mixture of V-7 and V-8. 2.0 ml of dry tetrahydrofuran was used for the transfer. The solution was stirred for five minutes at -78°, then for ten minutes at room temperature. The solution was cooled to -15° and formaldehyde was added via a stream of argon from another flask containing dry formaldehyde polymer (dried *in vacuo* over phosphorus pentoxide) heated at 148-150°. After 30 minutes the now milky white solution was added to 50 ml of water and extracted three times with 50 ml portions of dichloromethane. The combined organic extracts were washed with 50 ml of brine and dried over anhydrous magnesium sulfate. The solvents were removed *in vacuo* to give 22 mg (92%) of a 1:1 mixture of starting ketones V-7 and V-8 which was 90% pure by tlc.

B. Using Ethyl Formate

To a cold (-78°) solution of lithium diisopropylamine prepared from 0.10 ml (0.70 mmol) of dry diisopropyl amine and 0.15 ml (0.37 mmol) of a 2.50 M hexane solution

of n-butyllithium in 1.0 ml of tetrahydrofuran at -55° was added 25 mg (0.093 mmol) of a 1:1 mixture of V-7 and V-8 with 2.0 ml of dry tetrahydrofuran used for the transfer. The solution was stirred for five minutes at -78°, then for ten minutes at room temperature, and then 0.08 ml (1.0 mmol) of ethyl formate was added. The solution was stirred for 50 hours at room temperature, added to 50 ml of water, and extracted three times with 50 ml portions of dichloromethane. The combined organic extracts were washed with 50 ml of brine and dried over anhydrous magnesium sulfate. The solvents were removed in vacuo to give 25 mg (100%) of a 1:1 mixture of starting ketones V-7 and V-8 which was 95% pure by tlc.

Preparation of Ketones W-1 and W-3

A. From Ketone P-5

A solution of 2.25 g (10.9 mmoles) of ketone P-5, 1.3 g (34 mmoles) of lithium aluminum hydride, and 35 ml of dry pyridine was stirred for 10 minutes at 0° and then for 20 minutes at room temperature. The reaction was quenched with 1.3 ml of water, 1.3 ml of 10% aqueous sodium hydroxide, and 3.9 ml of water, and then filtered through anhydrous magnesium sulfate. The solvents were removed in vacuo to give 2.3 g of material which was combined with 2.72 g (21.6 mmoles) of oxalic acid dihydrate, 8.0 ml of water, and 100 ml of absolute methanol and stirred at room temperature.

After two hours the solution was treated with 2.29 g (21.6 mmol) of anhydrous sodium carbonate, added to 50 ml of water, and extracted three times with 50 ml portions of ether. The combined organic extracts were washed twice with 25 ml portions of brine and dried over anhydrous potassium carbonate. The solvents were removed *in vacuo*, and the residue was chromatographed on silica gel with 100% ether to give 930 mg (44%) of alcohol W-1 (R_f 0.25) as a colorless liquid: ir ($CHCl_3$) 3590 and 3440 (OH), 1655 (C=O), and 1604 cm^{-1} (C=C); nmr ($CDCl_3$) δ 1.21 (s, 3, CH_3), 5.79 (s, 1, vinyl).

B. From Homo-Wieland-Miescher Ketone 50

To a solution of 4.39 g (22.9 mmoles) of ketone 50 in 35 ml of absolute ethanol was added, over a 45 minute period, 278 mg (7.6 mmoles) of sodium borohydride in 30 ml of absolute ethanol. The solution was stirred for an additional 10 minutes, added to 100 ml of water, and extracted three times with 100 ml portions of ether. The combined organic extracts were washed with 100 ml of brine and dried over anhydrous magnesium sulfate. The solvents were removed to give 4.4 g (100%) of a yellow oil which by tlc consisted of 50% starting ketone 50, 25% of desired ketone W-1, and 25% of a material assigned the structure W-3 (R_f 0.3 with 100% ether).

C. From Ketone 50 and $LiAl(O\text{-}t\text{-}Bu)_3H$

A solution of 2.1 g (10.9 mmoles) of ketone 50, 13.8 g (54.5 mmoles) of lithium tri(t-butoxy)aluminum hydride, and 400 ml of dry tetrahydrofuran was stirred for 110 minutes at 0°, treated with 22 ml (55 mmoles) of 10% aqueous sodium hydroxide, stirred for 15 minutes at 0° and one hour at room temperature, and then filtered through 120 g of silica gel with 300 ml of ethyl acetate. Chromatography on silica gel with 100% ether furnished 910 mg of ketone W-1 (R_f 0.25) and 871 mg (41%) of ketone W-3 (R_f 0.3) as a colorless liquid: ir ($CHCl_3$) 3590 and 3440 (OH) and 1690 cm^{-1} (C=O); nmr ($CDCl_3$) δ 1.24 (s, 3, CH_3), 2.14 (s, 2, $w_{\frac{1}{2}}$= 3 Hz, allylic and α to carbonyl), 5.65 (d, 1, J= 2Hz, vinyl).

Preparation of Ketone W-2

A solution of 323 mg (1.66 mmoles) of ketone W-1, 0.27 ml (3.0 mmoles) of freshly distilled dihydropyran, 3 mg of p-toluenesulfonic acid monohydrate, and 6 ml of dry ether was stirred for five hours at room temperature, added to 50 ml of ether, washed twice with 50 ml of bicarb and once with 50 ml of brine, and dried over anhydrous potassium carbonate. The solvents were removed in vacuo to give 444 mg (96%) of ketone W-2 as a colorless liquid (R_f 0.48 with 100% ether): ir ($CHCl_3$) 1653 cm^{-1} (C=O); nmr ($CDCl_3$) δ 1.21 (s, 3, CH_3), 1.28 (s, 3, CH_3), 4.6

(s, 1, $w_{\frac{1}{2}}$= 7Hz, α to two oxygens), 5.78 (s, 1, $w_{\frac{1}{2}}$= 3 Hz, vinyl).

Dissolving Metal Reductions

A. Reduction of W-1

To a solution of 30 mg (5 mmoles) of lithium wire in 5 ml of dry ether and 60 ml of dry ammonia (distilled over sodium) was added, over a 30 minute period, 342 mg (1.76 mmoles) of ketone W-1 in 10 ml of dry ether. After an additional 20 minutes the reaction was quenched with anhydrous sodium benzoate (which was added until blue color disappeared) and then 0.25 g (5 mmoles) of ammonium chloride. The ammonia was allowed to evaporate and 25 ml of water was added. The aqueous solution was extracted with 50 ml of ether and then 15 ml of ether, and the ether extracts were washed separately twice with 20 ml portions of 10% aqueous sodium carbonate and twice with 20 ml portions of brine. The combined organic extracts were dried over anhydrous potassium carbonate, and the solvents removed *in vacuo* to give 328 mg (95%) of a 9:1 mixture (by vpc at 180°, X-2 eluted second) of *cis*:*trans* ketones (R_f 0.3 with 100% ether): ir ($CHCl_3$) 3612 (OH) and 1699 cm^{-1} (C=O); nmr ($CDCl_3$) δ 1.13 (s,3,CH_3).

B. Reduction of W-2

In essentially the same manner as the dissolving

metal reduction of W-1, 440 mg (1.58 mmoles) of ketone W-2 was reduced with 70 mg (10 mmoles) of lithium wire in 60 ml of dry ammonia and 15 ml of dry ether; 0.13 ml (1.4 mmoles) of dry t-butanol being added along with the ketone so as to serve as a proton source. After quenching with sodium benzoate and 0.5 g (10 mmoles) of ammonium chloride, the solution was worked up as before to give 416 mg (94%) of a material which was hydrolyzed with 20 mg of p-toluenesulfonic acid monohydrate in 7 ml of absolute methanol and 1.3 ml of dry tetrahydrofuran to give the same 9:1 cis:trans ratio as from the reduction of ketone W-1.

Hydrogenation Experiments

A. Hydrogenation of W-1

A solution of 89 mg (0.46 mmol) of ketone W-1, 10 mg of 10% palladium on charcoal, and 9 ml of glacial acetic acid was hydrogenated at room temperature under one atmosphere of hydrogen. After 25 hours the solution was filtered through celite, and the residue washed with ether. The solution was added to 100 ml of water, and extracted three times with 100 ml portions of ether. The combined organic extracts were carefully washed twice with 100 ml portions of bicarb and once with 100 ml of brine, and then dried over anhydrous magnesium sulfate. The solvents were removed in vacuo to give 81 mg (90%) of

a 2:1 cis:trans mixture (by vpc at 200°) with X-2 still the predominant isomer. The nmr still looked like one compound, but the tlc with 100% ether clearly showed two compounds: the cis isomer at R_f 0.3 and the trans isomer at R_f 0.4.

A similar hydrogenation of 130 mg (0.67 mmol) of ketone W-1 in 11 ml of glacial acetic acid containing 11 mg of 10% palladium on charcoal for 30 hours in a Parr shaker (at 3 atm.) at room temperature gave 111 mg (85%) of the same 2:1 cis:trans mixture (by vpc and tlc) as the hydrogenation in acetic acid at atmospheric pressure.

Hydrogenation of 50 mg (0.26 mmol) of ketone W-1 at atmospheric pressure and room temperature for 14 hours in 10 ml of absolute ethanol containing 12 mg of 10% palladium on charcoal and 1 ml of 10% aqueous sodium hydroxide gave, after work-up, 43 mg (85%) of a 3:2 mixture (by vpc and tlc) of cis:trans ketones.

B. Hydrogenation of Q-2

In a manner completely analogous to the hydrogenation of W-1, 40 mg (0.2 mmol) of ketone Q-2 in 9 ml of glacial acetic acid containing 11 mg of 10% palladium on charcoal was hydrogenated at atmospheric pressure and room temperature for 22 hours to give a quantitative yield of Q-4 (100% pure by vpc at 200° and tlc with 100% ether).

C. Hydrogenation of W-3 and W-4

Hydrogenation of 88 mg (0.45 mmol) of ketone W-3 in 7 ml of glacial acetic acid containing 10 mg of 10% palladium on charcoal with a Parr Shaker (at 3 atm.)at room temperature for 50 hours gave 44 mg (50%) of a 9:1 trans:cis ratio (by tlc in 100% ether) of ketones.

A similar hydrogenation of 34 mg (0.16 mmol) of ketone W-4 (prepared by deconjugation of 40 mg of ketone Q-2 by treatment with 3 ml of 1 M of potassium t-butoxide in t-butanol for 90 minutes at room temperature) in 10 ml of glacial acetic acid containing 10 mg of 10% palladium on charcoal with a Parr shaker (3 atm. pressure) at room temperature for 23 hours gave only 32 mg (92%) of starting ketone W-4 (100% pure by vpc at 200° and tlc with 100% ether).

Correlation with Exocyclic Olefin Q-9

A solution of 325 mg (1.66 mmol) of alcohol X-2, 0.6 ml (10.7 mmoles) of ethylene glycol, 6 mg of p-toluenesulfonic acid monhydrate, and 15 ml of dry benzene was refluxed for four hours with azeotropic removal of water, cooled, added to 50 ml of ether, and washed twice with 30 ml of bicarb and twice with 25 ml of brine. The aqueous layers were extracted with an additional 40 ml of ether, and the combined organic extracts dried over anhydrous potassium carbonate.

The solvents were removed *in vacuo* and the residue distilled at 113-116° (0.05 mm) to give 315 mg (77%) of ketal X-3: ir ($CHCl_3$) 3608 cm^{-1} (OH); nmr ($CDCl_3$) δ 0.95 (s, 3, CH_3), 3.88 (s, 4, ketal).

A solution of 314 mg (1.31 mmoles) of ketal X-3 in 15 ml of dry dichloromethane was treated with 25 ml of Collins reagent (prepared from 1.54 g of chromium trioxide, 50 ml of dry dichloromethane, and 2.5 ml of pyridine). The solution was stirred for 20 minutes at room temperature and then filtered through 25 g of alumina (activity III) with 75 ml of dichloromethane and 50 ml of ether. The solvents were removed *in vacuo* to give 284 mg (91%) of ketone X-3 as a colorless oil: ir ($CHCl_3$) 1689 cm^{-1} (C=O); nmr ($CDCl_3$) δ 1.17 (s, 3, CH_3), 3.88 (s, 4, ketal).

A solution of 283 mg (1.19 mmoles) of ketone X-3 in 9 ml of dry ether was added to a solution of 4.6 ml (7.1 mmoles) of a 1.55 M hexane solution of methyllithium in 6 ml of dry ether at 0° to -10° over 90 minute period. The solution was stirred for an additional 30 minutes at 0° and then for one hour at room temperature, added to 50 ml of water, and extracted twice with 50 ml portions of ether. The combined organic extracts were washed twice with 25 ml portions of brine and dried over anhydrous potassium carbonate. The solvents were removed *in vacuo* to give 298 mg (100%) of a 2:1 mixture (by vpc at 210°,

X-3 eluted first) of alcohol X-4 to starting ketone X-3. Treatment of the mixture with 14 ml (22 mmoles) of 1.55 M hexane solution of methyllithium in 28 ml of dry ether gave after work-up 300 mg (99%) of alcohol X-4 as a colorless liquid: ir ($CHCl_3$) 3598 cm^{-1} (OH); nmr ($CDCl_3$) δ 0.99 (s, 3, C-4a CH_3), 1.10 (s, 3, C-5 CH_3), 3.88 (s, 4, ketal).

To a solution of 300 mg (1.2 mmoles) of alcohol X-4 in 7.0 ml of dry pyridine at -15° was added 0.25 ml (3.5 mmoles) of thionyl chloride. The solution was stirred for 30 minutes at -10° to -15°, added to 25 ml ice and then to 25 ml of water, and extracted with 50 ml of ether. The organic layer was washed with 50 ml of bicarb, then 25 ml of water, and then 50 ml of brine. The aqueous layers were extracted with an additional 50 ml of ether, and the combined organic extracts dried over anhydrous potassium carbonate. The solvents were removed *in vacuo* to give 272 mg (96%) of Q-9 (95% pure by vpc at 200°).

3,3-Ethylenedioxy-16β-hydroxy-5-epi-18,19-dinoraphidicolane (Y-1) and 3,3-Ethylenedioxy-13α-hydroxy-5-epi-18,19-dinorstemodane (Y-2)

A solution of 400 mg (0.74 mmol) of a 65:35 mixture of brosylates T-2 to T-3, 210 mg (1.5 mmoles) of anhydrous potassium carbonate, 20 ml of water, and 40 ml of dioxane was heated for five hours at 48-52°, cooled, added to

400 ml of bicarb, and extracted twice with 400 ml portions of ether. The ether extracts were washed separately with 200 ml of brine and dried over anhydrous potassium carbonate. The solvents were removed in vacuo (using a cyclohexane azeotrope to remove the dioxane) and the residue chromatographed on silica gel with 95:5 ether:petoleum ether to afford 142 mg (60%) of alcohol Y-1 (R_f 0.3) as a white foam (solid at 0°) and 47 mg (20%) of alcohol Y-2 (R_f).2) as a white solid, mp 131-134°.

One recyrstallization from hexane and ether gave an analytically pure sample of Y-2 as a white solid, mp 140-141°: ir ($CHCl_3$) 3600 and 3450 cm^{-1} (OH); nmr ($CDCl_3$) δ 0.97 (s, 3, C-20 CH_3), 1.09 (s, 3, C-17 CH_3), 3.81 (s, 4, ketal).

Anal. Calcd for $C_{20}H_{32}O_3$: C, 74.96; H, 10.06. Found: C, 75.09; H, 10.14.

An analytically pure sample of alcohol Y-1 was prepared by bulb-to-bulb distillation at 146-148° (0.002 mm) to give a clear, colorless liquid: ir ($CHCl_3$) 3600 and 3480 cm^{-1}(OH); nmr ($CDCl_3$) δ 0.97 (s, 3, C-20 CH_3), 1.08 (s, 3, C-17 CH_3), 3.80 (s, 4, ketal).

Anal. Calcd for $C_{20}H_{32}O_3$: C, 74.96; H, 10.06. Found: C, 74.90; H, 10.88.

A solution of 2 mg (0.004 mmol) of brosylate T-2 (85%-90% pure) in 2 ml of dioxane and 1 ml of water

containing 1 mg of potassium carbonate was heated at 50° for five hours and worked up to give 1 mg of alcohol Y-1 (90% pure by tlc).

Dehydration of Alcohol Y-2

A solution of 4 mg (0.01 mmol) of alcohol Y-2, 2 ml of dry pyridine, and 0.02 ml (0.3 mmol) of thionyl chloride was stirred for 30 minutes at -15° to -20°, poured onto 25 ml of ice, and then treated with 25 ml of water and 50 ml of ether. The ether layer was washed with 25 ml of bicarb and 25 ml of brine and dried over anhydrous magnesium sulfate. The solvents were removed in vacuo to give 3 mg of olefin T-5 (100% pure by vpc at 250°).

5-Epi-18,19-dinoraphidicolan-3-one (Y-3)

A solution of 55.7 mg (0.174 mmol) of alcohol Y-1, 0.08 ml (1.1 mmoles) of thionyl chloride, and 4.0 ml of dry pyridine was stirred at -15° to -10° for 30 minutes, added to 25 ml of ice and then 25 ml of water, and extracted twice with 50 ml portions of ether. The ether extracts were washed separately with 50 ml of bicarb, 50 ml of water, and then 50 ml of brine, and were dried over anhydrous potassium carbonate. The solvents were removed in vacuo to give 53 mg (100%) of 3:1 mixture (by vpc at 250°, T-4 eluted first) of endocyclic olefin T-4

(the major isomer) and exocyclic olefin T-6.

The mixture was hydrolyzed by stirring with 87 mg (0.7 mmol) of oxalic acid dihydrate and 0.4 ml of water in 5.5 ml of absolute methanol for five hours at room temperature. The solution was quenched with 73 mg (0.7 mmol) of anhydrous sodium carbonate, added to 50 ml of water, and extracted four times with 50 ml portions of ether. The combined ether extracts were washed with 50 ml of brine and dried over anhydrous magnesium sulfate. The solvents were removed *in vacuo* to give 45 mg (100%) of ketone mixture T-8 and T-10.

The ketone mixture was hydrogenated at one atmosphere H_2 at room temperature for one hour in 15 ml of glacial acetic acid containing 20 mg of 10% palladium on charcoal. After one hour the solution was filtered through celite (the residue washed with ether), added to 100 ml of water, and extracted three times with 100 ml portions of ether. The combined ether extracts were carefully washed three times with 100 ml portions of bicarb and once with 100 ml of brine, and were dried over anhydrous magnesium sulfate. The solvents were removed *in vacuo* and the residue chromatographed on silica gel with 7:1 hexane:ethyl acetate to give 5 mg (11%) of starting olefins T-8 and T-10 (R_f 0.17) and 28 mg (62%) of ketone Y-3 (R_f 0.22) as a colorless liquid.

Bulb-to-bulb distillation at 108-110° (0.005 mm)

gave an analytically pure sample of Y-3 as a colorless liquid: ir ($CHCl_3$) 1720 cm^{-1} (C=O); nmr ($CDCl_3$) δ 0.75 (d, 3, J= 5.3 Hz, C-17 CH_3), 0.89 (s, 3, C-20 CH_3).

Anal. Calcd for $C_{18}H_{28}O$: C, 83.02; H, 10.84. Found: C, 83.20; H, 10.88.

18,19-Dinoraphidicolan-4-en-3-one (Y-7)

A solution 1 M in acetic anhydride and 10^{-2} M in perchloric acid was prepared by adding 4.8 ml (51 mmoles) of acetic anhydride and 0.06 ml (0.6 mmol) of 60% aqueous perchloric acid to 40 ml of ethyl acetate and diluting to 50 ml with additional ethyl acetate. A total of 3.0 ml of this solution was added all at once to 28 mg (0.108 mmol) of ketone Y-3. The resulting solution was stirred for five minutes at room temperature, added to 50 ml of ethyl acetate, washed with 50 ml of bicarb and then 50 ml of brine, and dried over anhydrous sodium sulfate. The solvents were removed in vacuo to give 32 mg (98%) of enol acetate Y-4 (R_f 0.45 with 7:1 hexane: ethyl acetate).

A solution of 32 mg (0.106 mmol) of the crude enol acetate Y-4, 0.03 ml of distilled epichlorohydrin, and 3 ml of carbon tetrachloride at 0° was treated dropwise with 1.0 ml (0.12 mmol) of a 0.12 M carbon tetrachloride solution of bromine. The solution (which went from yellow to orange in color) was stirred for ten minutes at 0°,

and then the solvents were removed *in vacuo* to give 36 mg (100%) of the bromo ketone mixture Y-6 (R_f 0.3 and 0.25 with 7:1 hexane:ethyl acetate).

A solution of 36 mg (0.106 mmol) of crude ketone Y-6, 35 mg (0.31 mmol) of semicarbazide hydrochloride, 35 mg (0.43 mmol) of anhydrous sodium acetate, and 9.3 ml of glacial acetic acid was heated at 68-72°. After two hours the solution was treated with 0.5 ml pyruvic acid dissolved in 1.0 ml of water and was heated for an additional two hours at 70°, cooled, and added to 100 ml of ether. The solution was washed six times with 100 ml portions of 5% aqueous sodium hydroxide and then twice with 50 ml portions of brine and was dried over anhydrous magnesium sulfate. The solvents were removed *in vacuo* and the residue chromatographed on silica gel with 3:1 hexane:ethyl acetate to give 21 mg (77%) of ketone Y-7 as a pale yellow liquid (R_f 0.27).

An analytically pure sample of Y-7 was prepared by bulb to bulb distillation at 98-102° (0.002 mm) to give a clear, colorless liquid: ir ($CHCl_3$) 1673 (C=O) and and 1618 cm^{-1} (C=C); nmr ($CDCl_3$) δ 0.75 (d, 3, J= 5.5 Hz, C-17 CH_3), 1.22 (s, 3, C-20 CH_3), 5.6 (s, 1, $w_{\frac{1}{2}}$= 4 Hz, vinyl).

Anal. Calcd for $C_{18}H_{26}O$: C, 83.67; H, 10.14. Found: C, 83.49; H, 9.97.

18,19-Dinoraphidicolan-3-one (Y-9)

To a solution of 15 mg (2.4 mmoles) of lithium wire, 2.0 ml of dry ether, and 30 ml of dry ammonia (distilled over sodium) was added 16 mg (0.062 mmol) of ketone Y-7 in 3.0 ml of ether over a ten minute period. The solution was stirred for an additional 20 minutes and quenched with sodium benzoate (until the blue color disappeared) and then with 128 mg (2.4 mmoles) of ammonium chloride. The ammonia was allowed to evaporate, and the solution was added to 75 ml of ether. The ether extract was washed with 50 ml of water, twice with 40 ml portions of bicarb, and twice with 35 ml portions of brine. The aqueous layers were extracted with an additional 50 ml of ether, and the combined organic extracts were dried over anhydrous magnesium sulfate. The solvents were removed *in vacuo* and the residue chromatographed on silica gel with 7:1 hexane:ethylacetate to give 4 mg (25%) of starting ketone Y-7 (R_f 0.11) and 10 mg (62%) of ketone Y-9 (R_f 0.25) as a white solid (vpc at 240° identical to that of Y-3), mp 104-108°.

One recrystallization from hexane and ether gave an analytically pure sample of ketone Y-9 as a white solid, mp 116-118°: ir ($CHCl_3$) 1710 cm^{-1} (C=O); nmr ($CDCl_3$) δ 0.75 (d, 3, J= 5.5 Hz, C-17 CH_3), 1.08 (s, 3, C-20 CH_3).

Anal. Calcd for $C_{18}H_{28}O$: C, 83.02; H, 10.84. Found: C, 82.96; H, 10.85.

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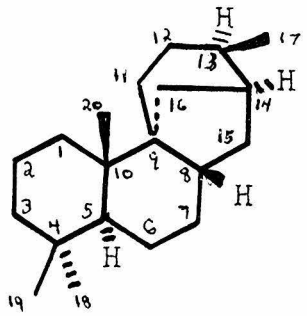

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