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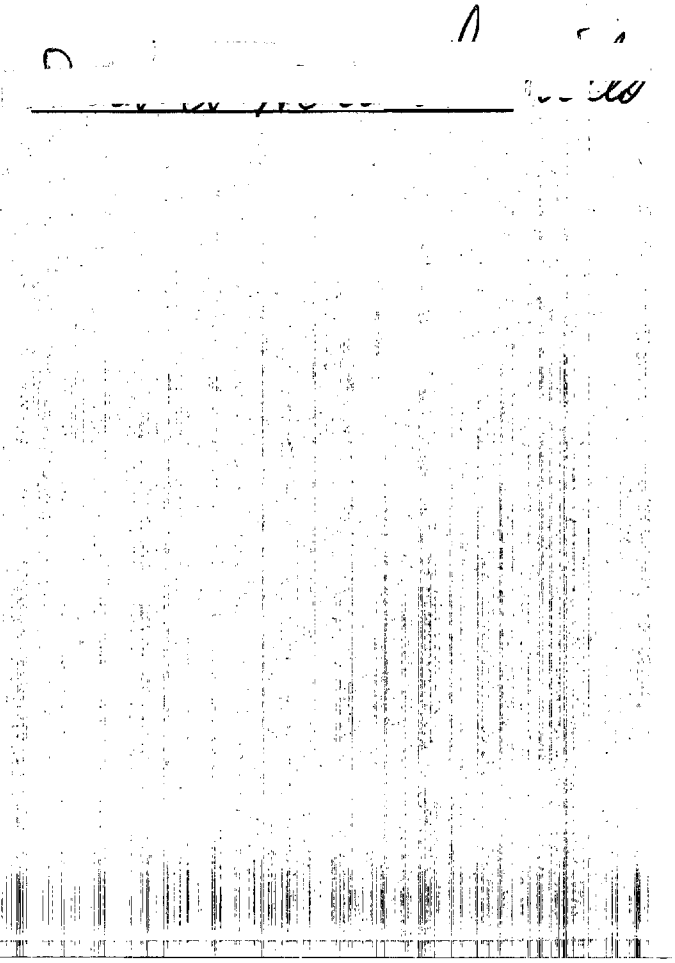

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THE SYNTHESIS OF TETRACYCLIC DITERPENOID ALKALOIDS AND RELATED DITERPENOIDS

A THESIS

Presented to

The Faculty of the Graduate Division

by

Delbert Howard Miles

In Partial Fulfillment

of the Requirements for the Degree

Doctor of Philosophy

in the School of Chemistry

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September, 1969

THE SYNTHESIS OF TETRACYCLIC DITERPENOID ALKALOIDS AND RELATED DITERPENOIDS

Approved:

Chairman

Date approved by Chairman: 9/19/69

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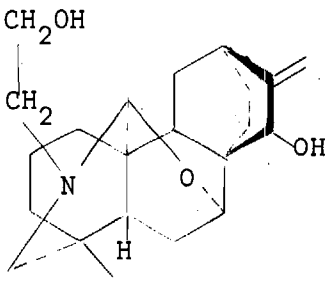
GLOSSARY OF ABBREVIATIONS

b.s.	broad signal
C	centigrade
CD	circular dischroism
cm^{-1}	wave numbers (infrared)
cps	cycles per second
d	doublet (NMR)
DMSO	dimethyl sulfoxide
g	gram(s)
GCQ	gas-chrom-Q
GLC	gas-liquid chromatography
GLC-MS	gas liquid chromatograph-mass spectrometer combination
H.F.R.	helium flow rate (GLC)
IR	infrared spectrum
m	multiplet (NMR)
M^+	molecular ion in mass spectrum
m/c	mass to charge ratio
mg	milligram(s)
min	minute(s)
ml	milliliters
m.p.	melting point
mu	millimicron
NMR	nuclear magnetic resonance
ORD	optical rotary dispersion

p.s.i.	pound per square inch (pressure)
R_t	retention time (GLC)
s	singlet (NMR)
t	triplet (NMR)
TLC	thin layer chromatography

SUMMARY

A sequence of reactions was performed, using podocarpic acid (53) as the starting material, in an attempt to synthesize (enantiomers) ajaconine (1) and atidine (2). Podocarpic acid (53) was converted to intermediate 106 by a 16-step reaction sequence that was similar to one



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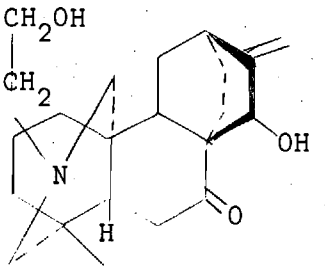

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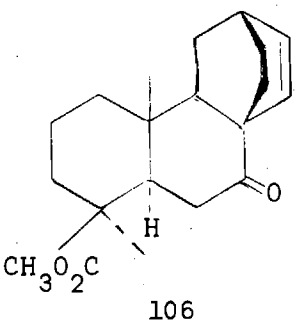
described by Zalkow and co-workers.[40] Intermediate 106 was converted to azide 118, which was photolyzed by procedures similar to those of



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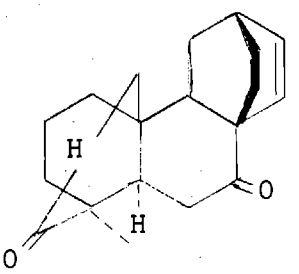
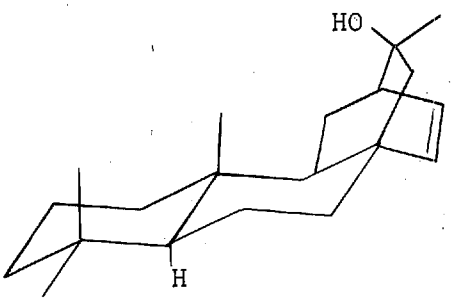


123

ApSimon and Edwards,[14] to give lactam 123. Lactam 123 should be readily convertible to dihydroajaconine by a five-step reaction sequence.

Intermediate 179, which was synthesized by Gabriel,[84] has been converted to isotrachylobane (151) by treatment with sodium borohydride and boron trifluoride-etherate in diglyme at low temperatures. The

product was contaminated with an impurity (25%) which showed similar properties.



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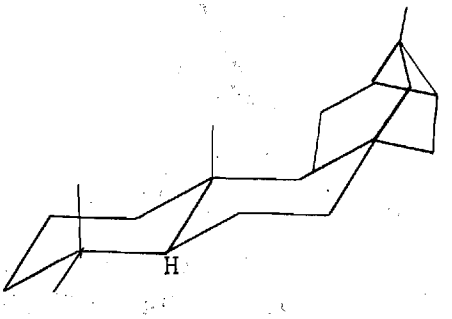


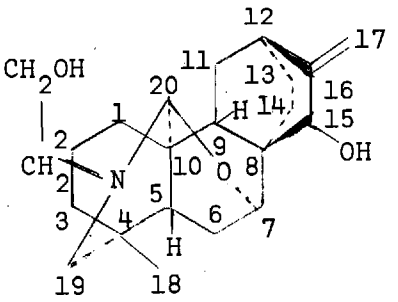
151

A number of compounds were isolated from *Sarracenia Flava* (Golden Trumpet) which is indigenous to the Okefenokee Swamp. Among these were acetovanillen (185) and a triterpene which has properties similar to betulin (196). The crude extract was shown to have anti-tumor activity by the National Cancer Institute.

CHAPTER I

INTRODUCTION

The text of this portion of this thesis is concerned with the development of synthetic sequences which will lead to the synthesis of the enantiomers of two diterpenoid alkaloids, ajaconine (1) and atidine (2).



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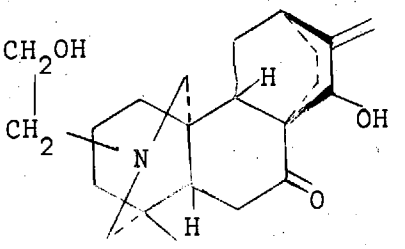

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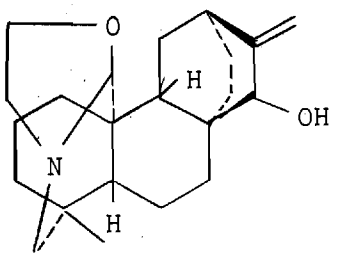
Ajaconine (1) has been isolated[1] from the extract of *Delphinium ajacis* seeds, as well as from *D. consolida*,[2] and atidine (2) has been isolated,[3] along with atisine (3), from *Aconitium heterophyllum*. The plants of *Delphinium* and *Aconitium* genera have intrigued and fascinated man for years because of their insecticidal properties, their poisonous effect on cattle, and their medicinal properties. The extract of *Aconitium heterophyllum* has been used as an expectorant, febrifuge, bitter tonic, and in Indian folk medicine.[2] Perhaps, it is this same type of fascination which accounts for the interest of organic chemists in these plants.



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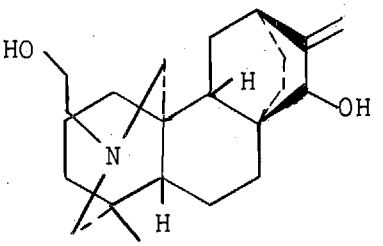

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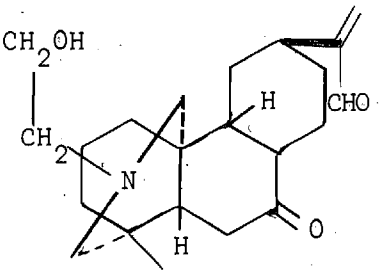

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The structure elucidation of atidine (2) was carried out in the following manner. Atidine (2) was characterized as a keto-diol. The carbon skeleton was established when Wolff-Kishner reduction of the keto group led to dihydroatisine (4).[4] Possible sites for the keto groups were indicated by observation that treatment of atidine (2) with alkali under mild conditions led to extensive formation of polymeric material.[2] With a keto group at either 7 or 14 one would expect the β-hydroxyketone to undergo facile cleavage of the retroaldol type to give the unstable acrolein derivative 5, thus accounting for the rapid destruction of atidine (2).

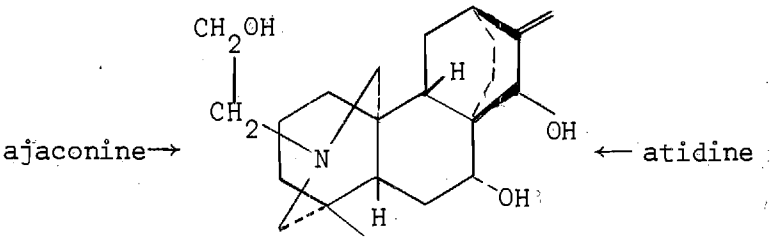

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Figure 1. Correlation of Atidine and Ajaconine

Subsequent correlation (see Figure 1) of atidine (2) and ajaconine (1) *via* dihydro derivative 6, and the elucidation of the structure of ajaconine (1),[5] allow the keto function to be assigned to position 7 in atidine (2).

Ajaconine (1) was related[5,6] (see Figure 2) to atisine (3) by degradation to a common azomethine base 7. The position of the allylic

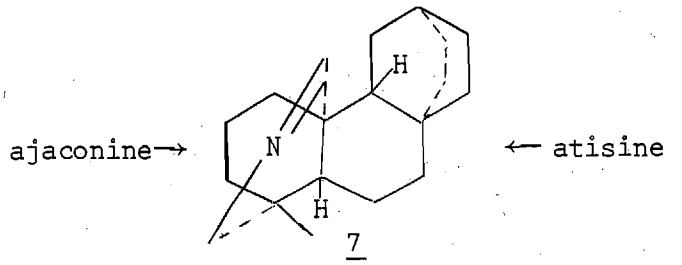

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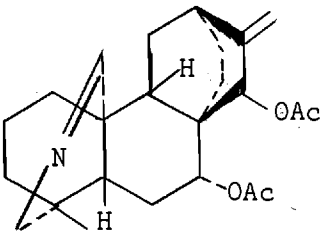
Figure 2. Correlation of Atisine and Ajaconine

alcohol system of ring D was clarified by the relationship to atidine (2), and thence dihydroatisine (4). When the carbinolamine ether system in ajaconine (1) was reduced with sodium borohydride, a dihydro base was obtained which formed a triacetyl derivative. This underwent the Hofmann-type elimination to give an azomethine base, which together with the high pk (11.3) and the formation of anhydronium salts led to the initial structure for ajaconine (1) containing an atisine-like oxazolidine ring. However, later work[5] showed that this involved the 7-oxygen atom. The position of the hydroxyl group on opening of the ether ring was established as follows.[6] The diacetoxyazomethine 8, obtained from Hofmann elimination, was oxidized to the C_{19} aceto-xynorketone 9. Wolff-Kishner reduction eliminated the oxygen functions on ring D and led to the azomethine mono-ol 10 which was converted



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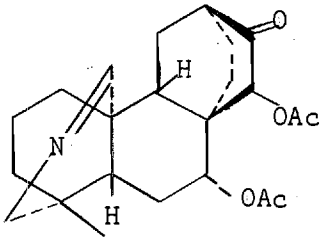

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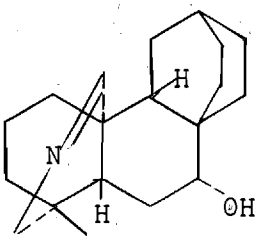

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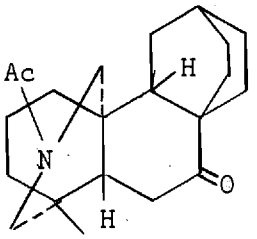
rationally to ketone 11. Upon bromination and dehydrobromination, ketone 11 formed the α,β-unsaturated, ketone 12 with spectral properties



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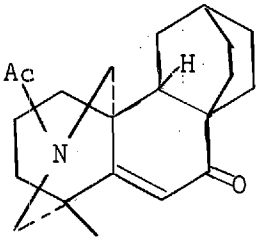

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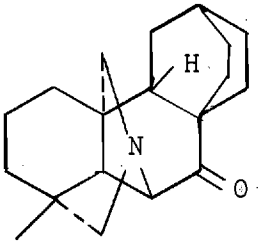
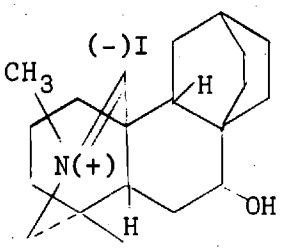


13

consistent with a ring B ketone. The ultraviolet spectrum (λ_{max} 250 mu, calc. 244 mu) showed an interaction with the nitrogen bridge. It is interesting to note that when ketone 11 was brominated and dehydrobrominated compound 13 was obtained as the major byproduct.

That the carbinolamine in ajaconine (1) is derived from the 7-oxygen was shown by the behavior of the methiodide 14 with strong base.[5] The product was a hydroxyl-free base 15 (pk'_a 10) and hence must be an internal cyclization product derived from the 7-hydroxyl and carbon 19 or 20. Since oxidation of 15 gave carbinolamine ether



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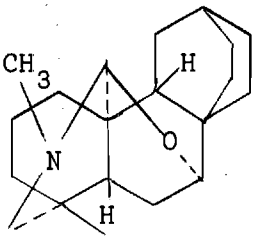

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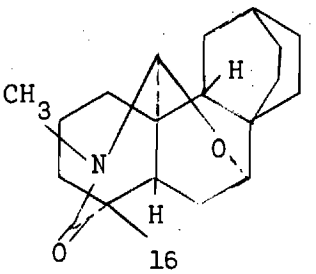

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lactam 16 with the amide carbonyl at C-19, it was clear that C-20 is involved in ether formation. The amide carbonyl was assigned to C-19 since, in no case, has it been possible to oxidize C-20 to a carbonyl with external reagents.[42]

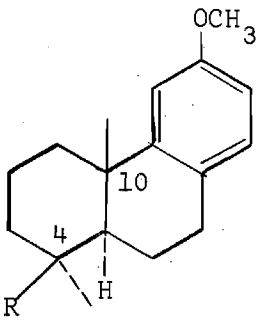
Studies in the synthesis of complex diterpenoid alkaloids have been chiefly concerned with the synthesis of the tetracyclic amine and bicyclo[2,2,2]octane systems.

Syntheses of atisine (3), a less complex alkaloid compared with ajaconine (1) and atidine (2), have been accomplished recently by four different groups.[7-13] Nagata and his associates[7] were the first group to describe the synthesis of atisine in racemic form. The synthetic intricacies of small portions of the molecule that were solved by these groups represent an extremely important contribution. However, with the exception of Wiesner's *et al.*,[13] these synthetic schemes do not have the flexibility necessary for the total synthesis of ajaconine (1) and atidine (2).

The two main approaches which have been developed for the synthesis of the E and F ring systems are photochemical insertion utilizing a *cis* C-4 acyl azide group and the C-10 methyl group and the

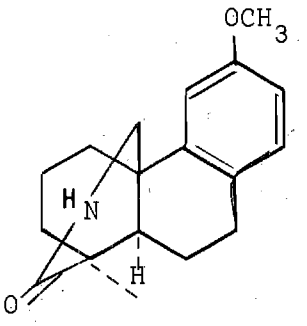
utilization of an already active C-10 group in ring A to give the nitrogen-containing E ring.

Edwards and ApSimon[14] utilized o-methylpodocarpic acid (17) in the development of the first approach. Photolysis of o-methylpodocarpic acid azide (18) was shown to yield the desired lactam 19. Lactam 19 was then converted by a rational sequence of reactions to compound 20. Two of the total syntheses [9,11,12] have incorporated this approach. Edwards and ApSimon[14] have further shown that compound 20 bears an enantiomeric relationship to the corresponding compound in the degradation of atisine (3). Hence, syntheses of ajaconine (1), atidine (2),



17, R = CO_2H

18, R = CON_3



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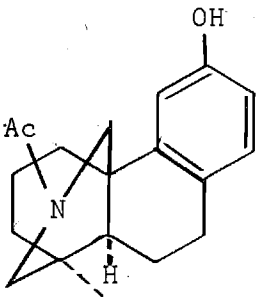
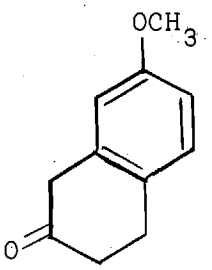


20

and atisine (3) from podocarpic acid would yield compounds bearing an enantiomeric relationship to the natural products.

Wiesner, Valenta and associates[15] have described another approach to this problem. They have been able to bridge ring A with a nitrogen containing ring by the introduction of a functional group at C-10 and then intramolecular acylation of C-4. The key intermediate 22 was synthesized by a rational sequence from compound 21. Compound 22 was

converted to 23 by an ingenious intramolecular cyclization. Preferential thioketalization followed by Raney-nickel treatment gave alcohol 24. Dialdehyde 25 was prepared by a three-step sequence, involving pyrolysis of the benzoate of 24, conversion of the resulting olefin to a diol with osmium tetroxide and cleavage of the diol with lead tetraacetate. Finally hydrogenation of the dioxime of dialdehyde 25 gave compound 26.



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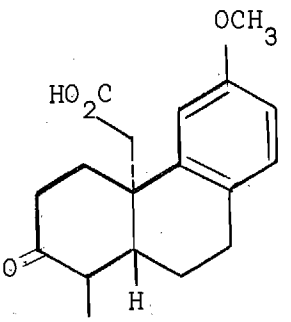

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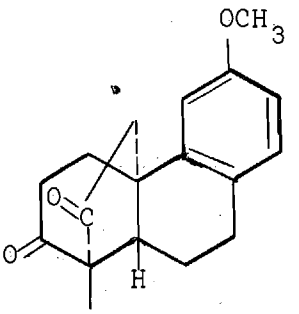

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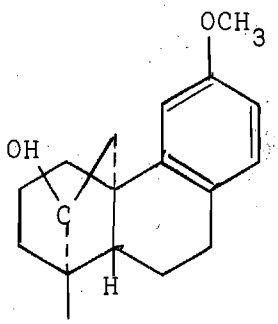

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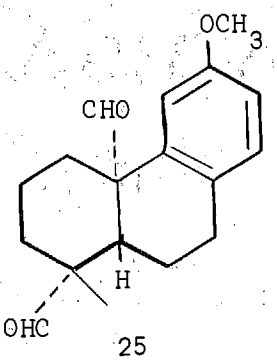

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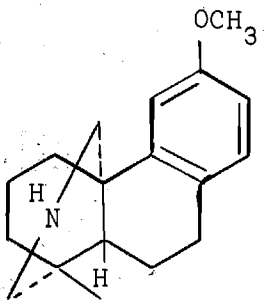
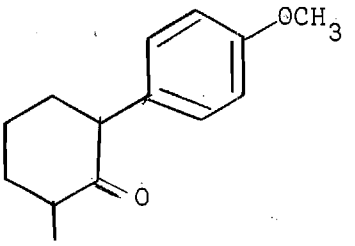


26

An elegant approach recently described by Iwai and associates[16] offers yet another path for incorporation of the nitrogen-containing E ring in a suitable carbocyclic system. This was achieved by the condensation of formaldehyde and methylamine with the ketone 27. When the resulting ketone 28 was condensed with lithium ethoxyacetylide, partially reduced, hydrolyzed in acid, and catalytically hydrogenated,

isomeric aldehydes 29 and 30 were obtained. The aldehydes were separately subjected to hydride-reduction and polyphosphonic acid-catalyzed cyclization yielded the tetracyclic amines 31 and 32. This approach, though elegant, suffers from lack of stereospecificity at C-5.



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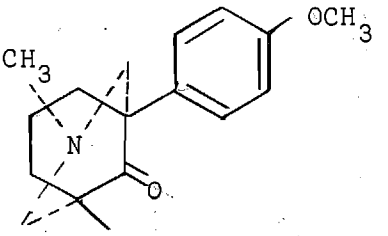

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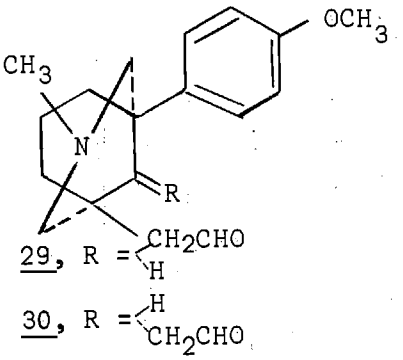
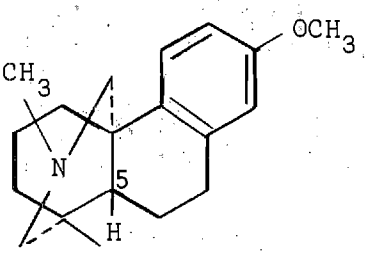
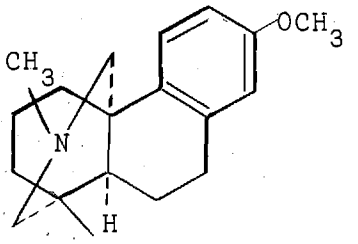


29, R = 30, R =



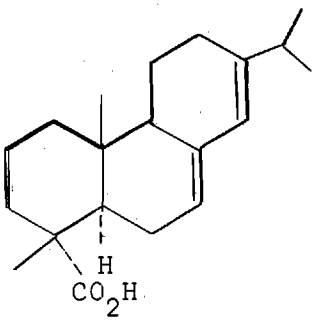
31



32

Another successful approach by Tahara and associates[10,11,17] involved the synthesis of ketolactone 34 from abietic acid (33). Ketolactone 34 was converted by a three-step sequence into anhydride 35 which gave keto-imide 36 when heated with urea. When reduced with lithium aluminum hydride, acetylated, and selectively saponified, compound 36 yielded 37. Tahara *et al.*[10,17] have converted 37 into 38,

which in turn has already been transformed[8,9,12] into atisine (3). Thus this constitutes a total synthesis of atisine (3).



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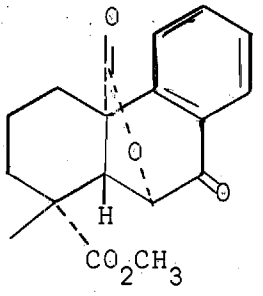

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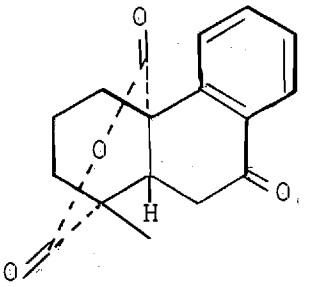

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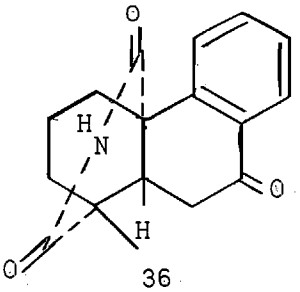

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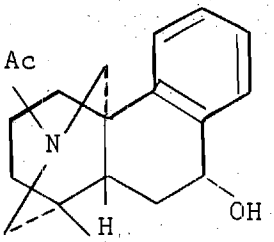

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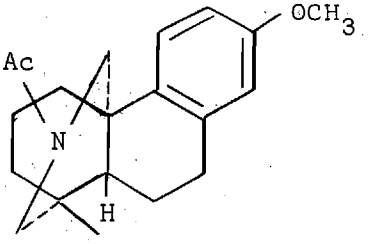
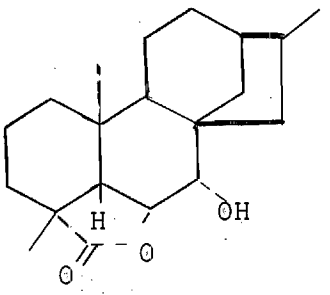


38

Barton and associates[18] have constructed the E and F ring systems by the photolysis of the nitrite ester of 39. However, the product, lactam 40, could not be successfully converted into the carbinol-amine ether system contained in ajaconine (1).



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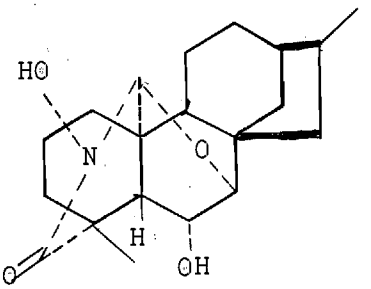
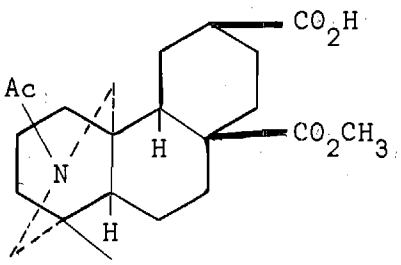


40

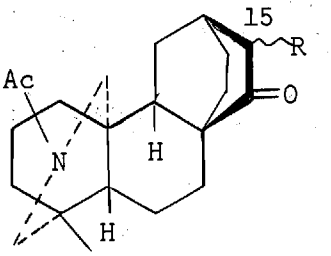
Barton *et al.*,[18,19] Akhtar *et al.*,[20] Wettstein *et al.*[21,22] have contributed a large quantity of material which could be useful during the consideration of methods for the construction of the ether bridge (F ring in ajaconine). Utilizing a variety of reagents, such as lead tetraacetate, silver acetate, and mercuric oxide under thermal and photolytic conditions, these workers have been able to construct the equivalent of the F ring system of ajaconine in steroid systems.

Four completely different approaches have been developed for the construction of the bicyclo[2.2.2]octane C, D ring system contained in ajaconine (1), atidine (2), and atisine (3).

Pelletier and Parthasarathy[23] have described the conversion of monocarboxylic ester 41, a degradation product of atisine (3), into amino alcohol 45 which had already been reconverted[24-26] into the parent alkaloid 3.

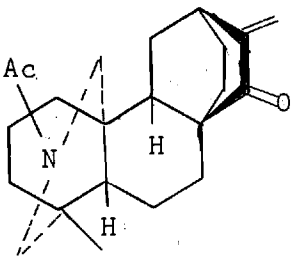


41

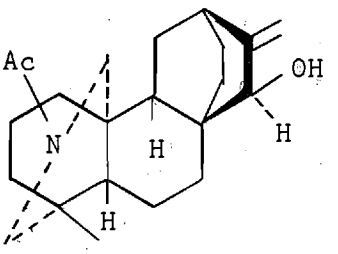


42, R = H

43, R = CH_3



44

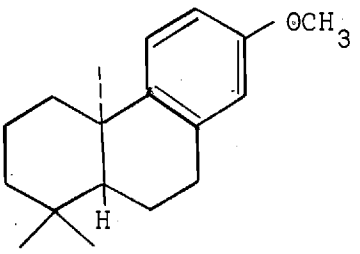


45

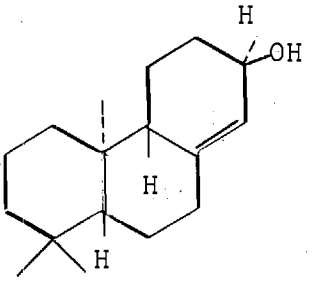
The reaction sequence for the reconstruction of the bicyclooctane system, involved one carbon homologation of the secondary carbonyl group *via* the Arndt-Eistert reaction, followed by ring closure of the *cis* oriented ester functions in a Dieckmann cyclization and finally, hydrolysis and decarboxylation to give 42. Compound 43 was obtained, as a mixture of epimers at C-15, when ketone 42 was methylated in the presence of sodium hydride in dimethyl sulfoxide. The α,β unsaturated ketone 44 was obtained by bromination and dehydrobromination of ketone 43. Reduction of the C-16 keto group gave a mixture of allylic alcohols from which the desired isomer 45 was separated.

Ireland and Bell[27] followed a different approach in the synthesis of the C/D ring system. This successful pursuit involved the use of allylic alcohol 47, which was obtained by lithium-ammonia and hydride reduction of racemic 46. The reaction of 47 with ethyl-vinyl ether and subsequent pyrolysis of the vinyl ether afforded 48. The desired activation of the C-12 methylene was achieved by preparation of an acetal ketone via hydroboration-oxidation of the ethylene acetal of 48. Ring closure was effected by acid-catalyzed aldol-type condensation. Wolff-Kishner reduction of the tetrahydropyranyl ether of the resulting alcohol 49, followed by acid-catalyzed cleavage of the ether moiety, Jones oxidation, treatment with methylenetriphenylphosphorane, allylic bromination, and finally reduction with lithium aluminum hydride afforded the desired endocyclic isomer 50. Photosensitized oxidation of 50, followed by reduction of the allylic peroxides led to a separable mixture of two epimeric alcohols, 51 and 52. No stereochemical assign-

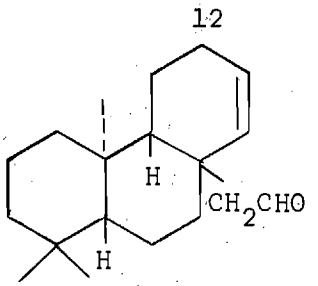
ments to the two epimers were made, but the presence of each in the reaction mixture assured the success of this method.



46



47



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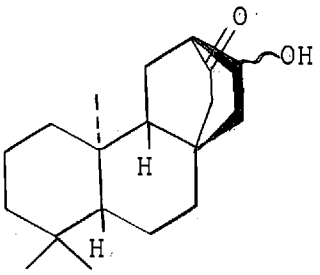

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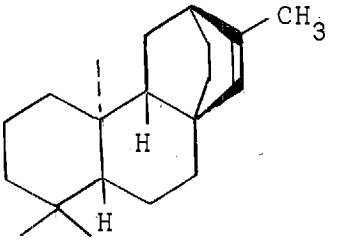

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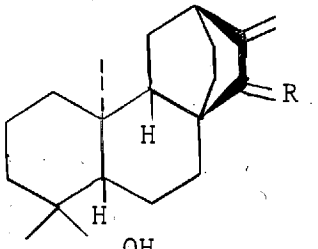
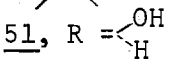
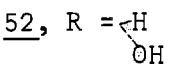
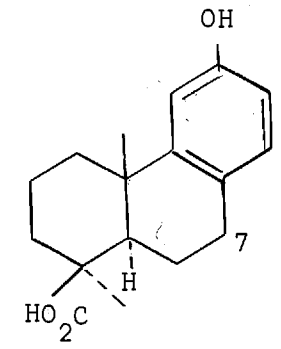


51, R = 

52, R = 

Zalkow and Girotra[28-32] used abietic acid (33) and podocarpic acid (53), both of which have been totally synthesized,[33-36] in a completely different approach. Enone 54, prepared from methyl-o-methyl podocarpate,[37] provided diacetate 55 which was pyrolyzed to a diene mixture. Adduct 56[32] was obtained by Diels-Alder addition to the diene mixture. Compound 57 was obtained from adduct 56 by a four-step sequence which provided a bicyclo[2.2.2]octane ring system useful for the introduction of the D ring substituents. The feasibility of this approach is further emphasized by earlier work[30] on maleopimaric acid (58), which resulted in the synthesis of the isoprenoid skeleton 59, the racemic isomer of which has been converted into the C, D ring system of atisine (3) by Ireland and associates.[27] The diterpene atisirene (59),

recently isolated by Sukh Dev *et al.*[38] from *Erthroxylon monogynum* has been found to be the enantiomer of 59 which was previously synthesized by Zalkow and Girotra.[30]



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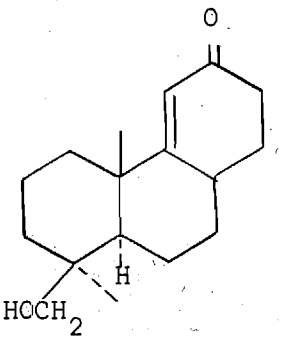

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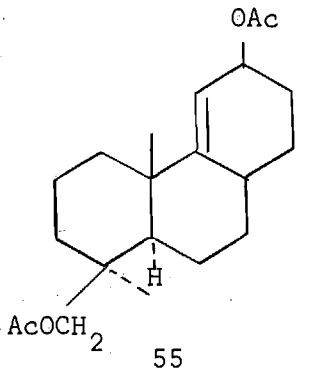

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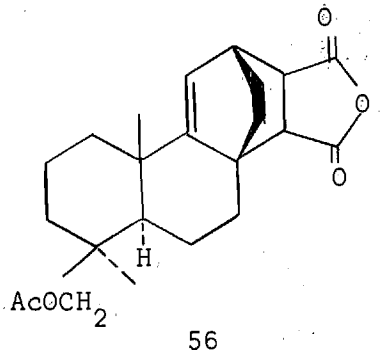

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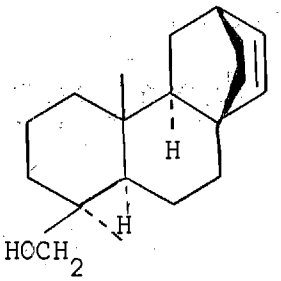

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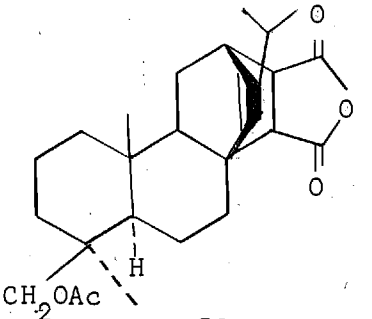

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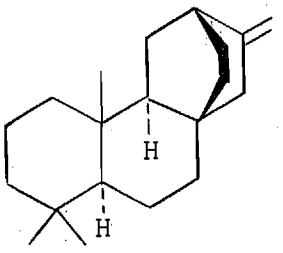

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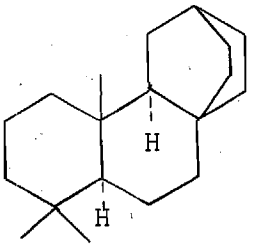

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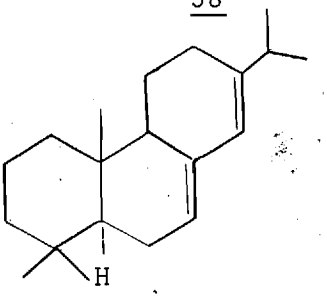


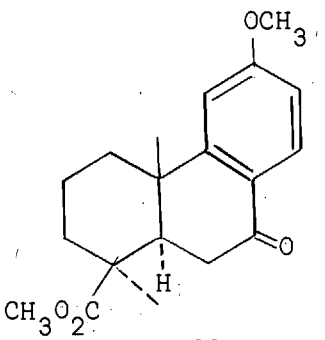
61

Ayer and associates[39] have synthesized the tetracyclic hydrocarbon 60 from abietic acid (33) in a sequence similar to that of Zalkow and Girotra.[28] The C/D ring system was constructed by a Diels-Alder reaction between compound 61 and maleic anhydride. The synthesis of 60 has also provided more confirmatory evidence concerning the

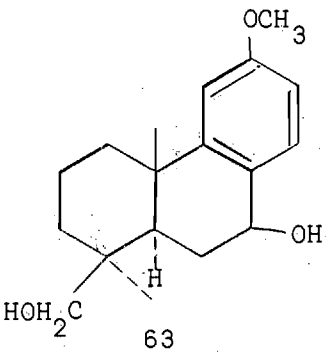
absolute configuration of atisine, since 60 is enantiomeric with the same hydrocarbon obtained from atisine.[39]

Zalkow and associates[40] have recently reported the synthesis of tetracyclic intermediates, from podocarpic acid (53), which are potentially useful in the synthesis of ajaconine (1) and atidine (2).

Since C-7 is the benzylic position in podocarpic acid, the most advantageous time to introduce the oxygen function would be while the C-ring is aromatic. Therefore methyl-o-methyl 7-ketopodocarpate (62) was prepared as previously described by Wenkert and associates.[41] The aromatic C-ring was then utilized to construct the bicyclo[2.2.2]octane system in a manner similar to that reported by Zalkow and Girotra.[31,32] Accordingly, after 62 had been reduced with lithium aluminum hydride to give diol 63, reduction with sodium in ethanol, tetrahydrofuran, and liquid ammonia followed by hydrolysis in methanolic hydrochloric acid gave dienone 64. Reduction of 64 with sodium borohydride followed by



62



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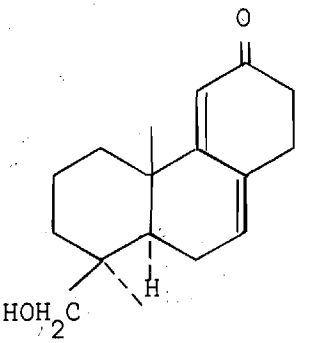
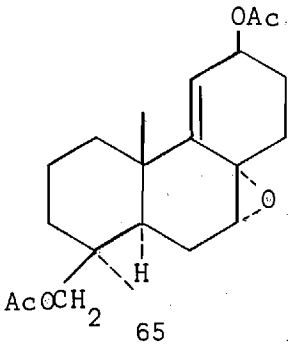


64

acetylation gave the diacetate, which on treatment with m-chloroperbenzoic acid gave epoxydiacetate 65. Treatment of 65 with boron trifluoride-etherate gave ketone 66 which after chromatography on alumina gave dienone 67.



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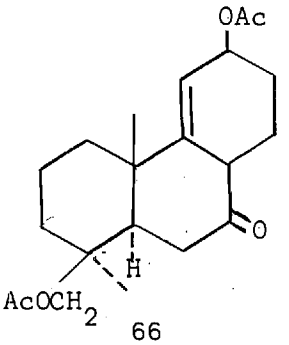

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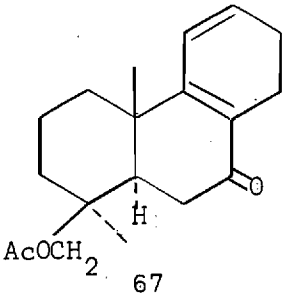
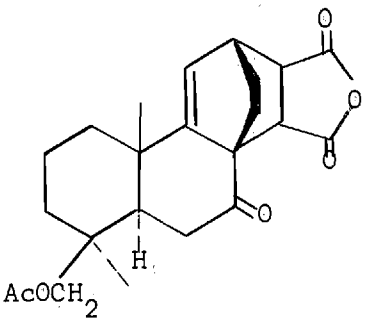


67

On treatment with maleic anhydride in refluxing toluene, 67 gave adducts 68 and 69. Treatment of 68 with diazomethane followed by



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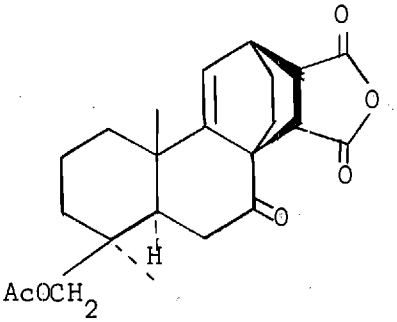

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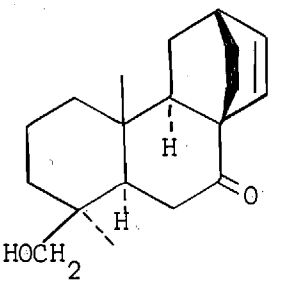


70

saponification, hydrogenation, and decarboxylation gave 70 which is a key intermediate in the synthesis of atidine (2) and ajaconine (1) and should be convertible into these alkaloids by procedures previously described in this introduction.[12,14,32,42]

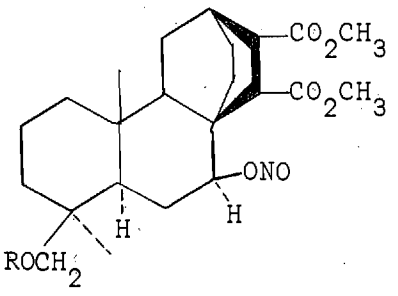
CHAPTER II

DISCUSSION OF RESULTS

As stated previously in the introduction, the goal of this portion of this thesis was the development of a general synthetic approach to a number of diterpenoid alkaloids, in particular, ajaconine (1) and atidine (2).

The first study undertaken was concerned with the attempted construction of the heterocyclic rings in ajaconine (1) using adduct 69, as a model, which was readily available as a by-product from the synthesis of 68.

The approach envisaged was the synthesis of nitrite ester 71 and subsequent photolysis, in a manner similar to that of Barton,[18] to give compound 72. Compound 72 could then be converted easily to compound 73 containing the E and F rings of ajaconine.



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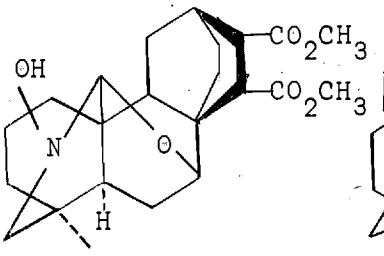

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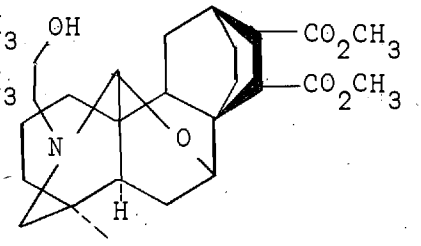
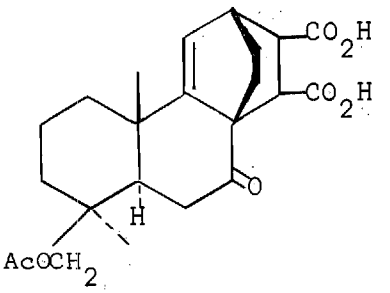


73

Initially, it was thought the synthesis of nitrite ester 71 would be achieved *via* direct hydrogenation of anhydride 69.

Hydrogenation of anhydride 69 was attempted with 5 per cent Pt/C in acetic acid and in ethyl acetate without success as shown by the continued presence of a vinyl proton doublet (J = 7 cps) at δ 5.68. Since hydrogenation of epimerized diacid 74[40] had been successful, it was proposed that the following sequence of reactions (see Figure 3) would



74

provide a suitable pathway to nitrite ester 71.

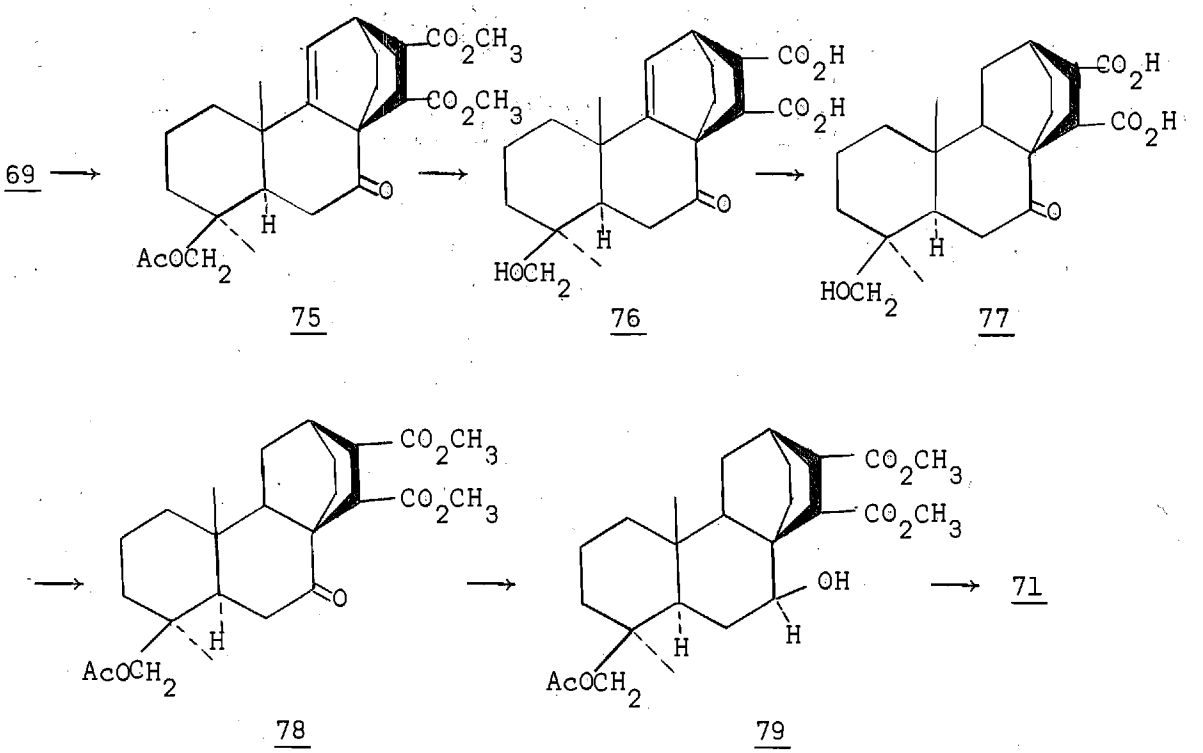


Figure 3. Proposed Scheme for the Synthesis of Nitrite Ester 71

Esterification of anhydride 69 with diazomethane in ether gave diester 75 in non-crystalline form, the infrared spectrum of which showed absorptions at 1740 cm^{-1} for esters, 1700 cm^{-1} for a ketone, and 1625 cm^{-1} for a double bond, while the NMR spectrum showed two tertiary methyl singlets at δ 1.28 and δ 1.51, a singlet at δ 2.20 for the acetate group, two singlets at δ 3.46 and δ 3.51 for the methoxy groups, and a doublet (J = 7 cps) at δ 5.78 for the vinyl proton.

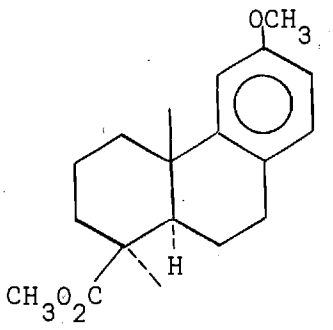
Diacid 76 was formed by saponification of 75 with sodium hydroxide in 50 per cent aqueous methanol solution. The non-crystalline glassy diacid 76 showed absorptions in the infrared spectrum for an acid (3600 -2400, 1700 cm^{-1}), an alcohol (3450 cm^{-1}), and a double bond, (1650 cm^{-1}). The NMR spectrum exhibited resonance signals at δ 0.89 and δ 1.08 (tertiary methyl group), δ 4.88 (hydroxyl proton), and δ 5.65 (vinyl proton doublet, J = 7 cps).

Hydrogenation of diacid 76 was attempted with 5 per cent Pt/C in acetic acid at atmospheric pressure and room temperature using varying concentrations of the catalyst and different reaction times. That all attempts were fruitless was evidenced by the lack of disappearance of the vinyl proton signal at δ 5.68 in the NMR spectrum. Also, the tetranitromethane test[44] for unsaturation gave a positive yellow color. The approach outlined in Figure 3 was not pursued further because of the difficulties encountered in the attempted hydrogenation of diacid 76.

Attention was directed toward the total synthesis of ajaconine (1) and atidine (2) *via* intermediate 70 as described in the introduction.[40] Consequently, podocarpic acid (53) was methylated with dimethylsulfate in methanolic-aqueous sodium hydroxide solution to give

methyl-o-methyl podocarpate (80). Oxidation of 80 with chromic anhydride in acetic acid gave methyl-o-methyl 7-ketopodocarpate (62).

The synthetic sequence outlined by Zalkow and associates[40] was modified at this point in order to eliminate an undesirable oxidation step that would have to be performed later in the sequence on intermediate 70. The carbonyl functionality at C-4 was retained by reducing compound 62 with sodium borohydride, instead of lithium aluminum hydride, to give crystalline ester-alcohol 81, m.p. 100-106°C. The infrared spectrum of 81 showed absorptions for an alcohol (3500 cm^{-1}), an ester (1715 cm^{-1}), and an aromatic system (1615 cm^{-1}). The NMR spectrum showed signals at δ 0.87 and δ 1.30 for two tertiary methyl groups, δ 3.81 for the methoxy group, and δ 6.81 (multiplet) for the three aromatic protons. The mass spectrum gave the parent ion at M^+ = 318 (calcd. for $C_{19}H_{26}O_4$; M^+ = 318).



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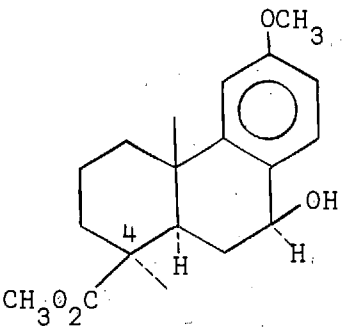
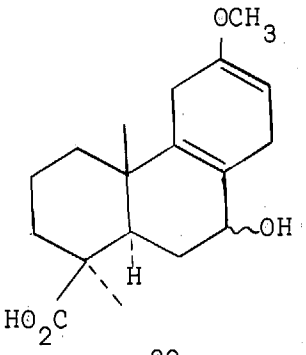


81

Birch reduction of alcohol 81 in sodium-liquid ammonia solution with tetrahydrofuran as the solvent, and ethanol as the proton source gave intermediate alcohol 82 which underwent acid hydrolysis of the enol ether and dehydration of the alcohol in concentrated hydrochloric

acid-methanol solution to give a crude mixture of products.



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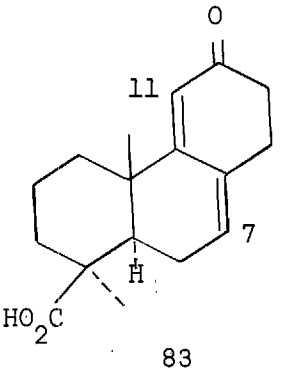

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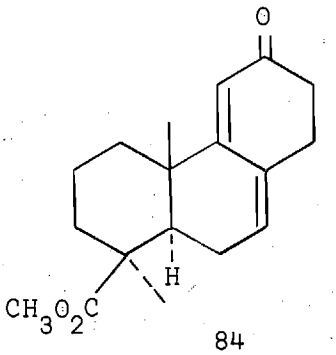
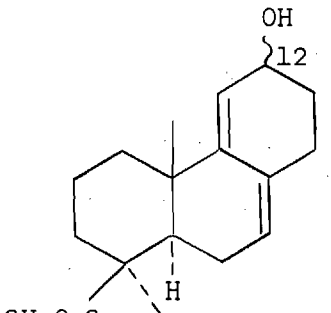


84

Separation of ketonic material was achieved by using Girard's "T" reagent. Consequently, crystalline dienone 83, m.p. 200-202°C., was obtained in approximately 60 per cent yield. The infrared spectrum of 83 showed absorptions at 3500-2500 cm^{-1} and 1700 cm^{-1} for a carboxylic acid, 1640 cm^{-1} for an α,β-unsaturated ketone, and 1575 cm^{-1} for a conjugated double bond. The NMR spectrum of 83 gave singlets at δ 1.03 and δ 1.29 for the tertiary methyl groups, a sharp singlet at δ 5.94 for the C-11 proton, and a broad signal at δ 6.15 for the C-7 proton, and a broad signal at δ 8.70 for the acid proton. The mass spectrum showed the parent ion at M^+ = 274 (calcd. for $C_{17}H_{22}O_3$; M^+ = 274).

Esterification of dienone 83 with diazomethane in ether gave crystalline 84, m.p. 110-111°C. The infrared spectrum showed absorption at 1710 cm^{-1} for an ester, 1650 cm^{-1} for an α,β-unsaturated ketone, and 1570 cm^{-1} for conjugated double bonds. The NMR spectrum of 84 showed two singlets at δ 0.97 and δ 1.24 for the two tertiary methyl groups, a sharp singlet at δ 5.90 for the C-11 vinyl proton, and a broad signal at δ 6.15 for the C-7 proton. The mass spectrum showed the parent ion at M^+ = 288 (calcd. for $C_{18}H_{24}O_3$; M^+ = 288).

Sodium borohydride reduction of dienone 84 gave non-crystalline alcohol 85. The infrared spectrum of 85 gave absorptions at 3350 cm^{-1} for a hydroxyl group, 1700 cm^{-1} for an ester carbonyl, and 1650, 1600 cm^{-1} for a conjugated diene system. Treatment of alcohol 85 with acetic anhydride in pyridine furnished acetate 86 as a non-crystalline material. Crystallization of 85 and 86 probably failed because of the existence of epimeric groups at C-12. The infrared spectrum of 86 showed absorptions for an ester (1710 cm^{-1}), an acetate (1710 and 1250 cm^{-1}), and for double bonds (1600 cm^{-1}). The NMR spectrum of 86 exhibited resonance signals at δ 0.84 and δ 1.20 (tertiary methyl groups), δ 2.08 (acetate), δ 3.69 (methoxy group), and δ 5.50 (multiplet for the C-7 and C-11 protons).



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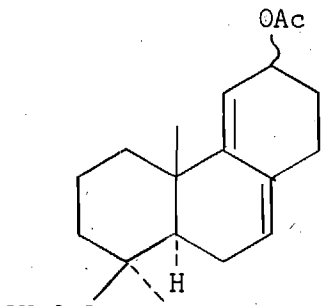

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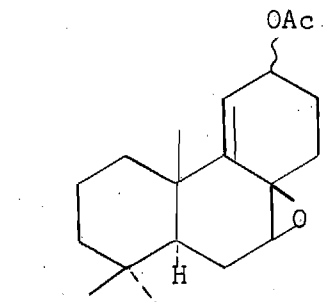
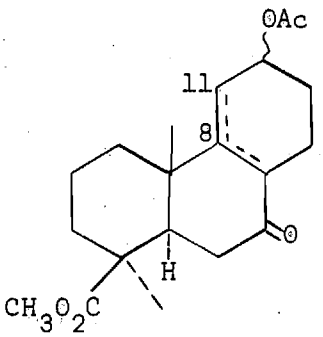


87

Selective epoxidation of 86 with m-chloroperbenzoic acid in dry ether gave non-crystalline epoxide 87. The infrared spectrum of 87 showed absorptions at 1720 cm^{-1} for the ester and acetate groups and at 1640 cm^{-1} for the double bond. The NMR spectrum gave signals for one of the tertiary methyl groups (δ1.18), an acetate group (δ2.08), an epoxide proton (δ 3.48, d of d, J = 7 cps), a methoxy group (δ3.68), and a vinyl proton (δ5.80, doublet, J = 6 cps). There were several

peaks in the methyl region δ 0.80 - 1.10 which were due to the other methyl group present in the various isomers. That compound 87 was obtained instead of the compound with the double bond at C-8,11 was evidenced by the fact that the vinyl proton was a doublet instead of a doublet of doublets or triplet. Crystallization attempts finally gave a few milligrams of a crude yellow solid, m.p. 158-161°C., which could not be purified further. The mass spectrum of crude epoxide gave a parent ion at M^+ = 348 (calcd. for $C_{20}H_{28}O_5$; M^+ = 348).

Isomerization of epoxide 87 with boron trifluoride-etherate in dry benzene gave ketone 88 in a non-crystalline form. The infrared spectrum showed absorptions at 1710 cm^{-1} (strong) for the ester, acetate, and ketone functions, 1650 cm^{-1} (medium) for an α,β-unsaturated ketone, and 1550 cm^{-1} for a double bond. The medium absorption for an α,β-unsaturated ketone seemed to indicate that the product was a mixture of two isomers with the double bond being conjugated with the ketone in one and at the C-8,11 position in the other. Dienone 89 was prepared by isomerization of the double bond and elimination of the acetate group on an alumina column (Merck, acid-washed, activity II). The overall yield of 89, m.p. 91-92°C, from 83 was approximately 50 per cent. The infrared spectrum of 89 gave absorptions



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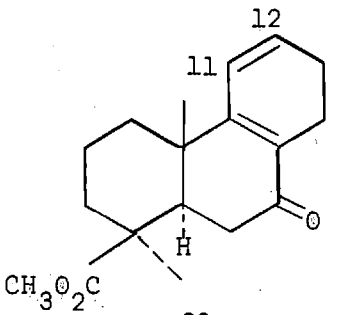
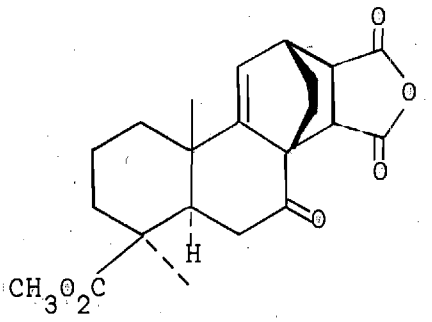


89

at 1725 cm^{-1} for a carboxylic ester, 1650 cm^{-1} for an α,β-unsaturated ketone, and 1550 cm^{-1} for conjugated double bonds. The NMR spectrum exhibited resonance signals at δ 0.99 and δ 1.27 (tertiary methyl groups), δ 3.72 (methoxy group), and δ 6.30 (broad signal for the two C-11,12 vinyl protons). The ultraviolet spectrum showed a maxima at 296 mμ with an extinction coefficient of 9,100 which was characteristic of a dienone system. The mass spectrum gave the parent ion at $M^+ = 288$ (calcd. for $C_{18}H_{24}O_3$; $M^+ = 288$).

A Diels-Alder reaction involving dienone 89 and maleic anhydride in m-xylene containing a trace of trichloroacetic acid gave adducts 90 and 91. GLC analysis showed the presence of 90 and 91 (1:1 ratio) in approximately 50 per cent yield and with R_t 3.6 and 4.6 minutes, respectively. Crystallization from ether yielded a white solid, m.p. 91-92°C, which was shown by GLC analysis to contain adducts 90 and 91 in a 1:1 ratio. The infrared spectrum of the mixture showed absorptions at 1840 cm^{-1} and 1770 cm^{-1} for an anhydride, 1710 cm^{-1} for the ester and ketone, and 1600 cm^{-1} for a double bond. The NMR spectrum of 90 and 91 showed signals at δ 0.85, 0.98, 1.21, 1.25 (tertiary methyl groups), δ 3.69 (methoxy group), and δ 6.11 (one vinyl proton doublet, J = 7 cps).



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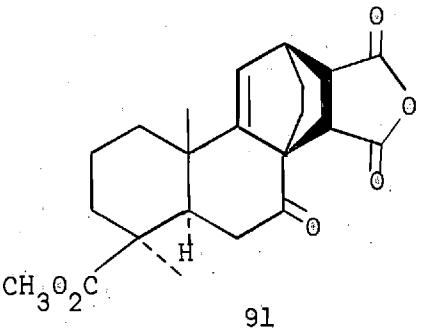
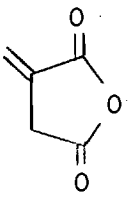


91

An attempt was made to determine the optimum conditions for the Diels-Alder reaction between dienone 89 and maleic anhydride. The yields obtained in all of the reactions carried out were comparable.

It was thought that if a Diels-Alder reaction could be executed successfully with either itaconic anhydride (92) or citraconic anhydride (93), intermediate 94 could be obtained readily. This would insure partial functionalization of the C/D ring system and would eliminate several steps in the proposed synthetic sequence. All attempts to achieve a reaction between these dienophiles and dienone 89 failed as evidenced by the lack of appearance of any new peaks in the GLC chromatogram.

Efforts were then directed toward the possible use of α-acetoxyacrylonitrile (95) as a dienophile in a manner employed by Bartlett and co-workers.[45] A successful reaction between dienone 89 and α-acetoxy-



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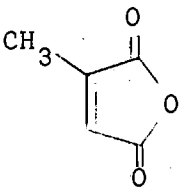

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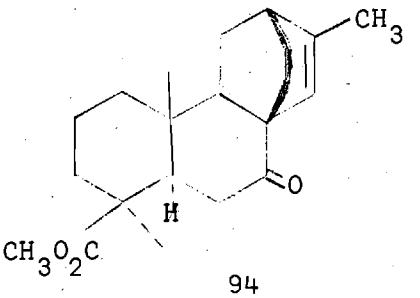

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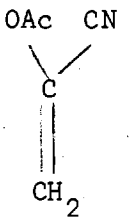

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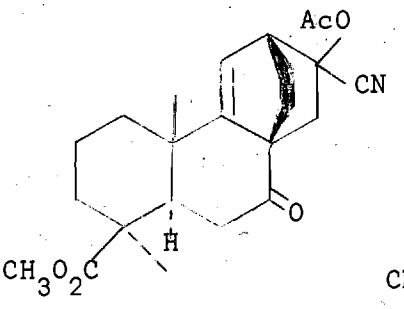

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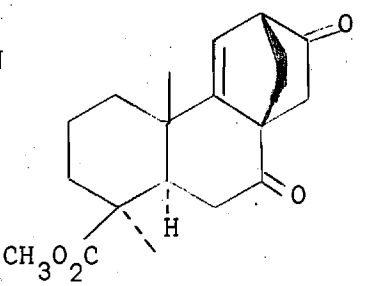
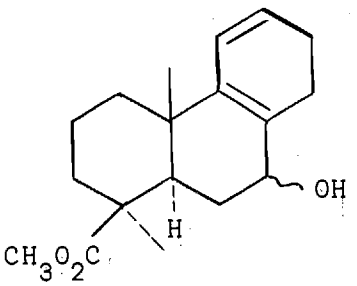


97

acrylonitrile (95) would furnish adduct 96 as one of the four possible iomers, which, when treated with base under the conditions described by Bartlett and co-workers,[45] would yield adduct 97. When this reaction was attempted in toluene solvent, GLC analysis showed the presence of only starting material.

It was thought that the Diels-Alder reaction might be more successful with a different diene system. With this in mind, dienone 89 was reduced with sodium borohydride to give diene 98 as a non-crystalline material. The infrared spectrum of 98 showed absorptions at 3600-3100 cm^{-1} for a hydroxyl group, 1725 cm^{-1} for a carboxylic ester, and 1630, 1600 cm^{-1} for the conjugated diene system. A successful reaction between the new diene, 98, and α-acetoxyacrylonitrile 95 would yield adduct 99. However, when this reaction was attempted under a variety of conditions, GLC analysis showed no formation of adducts.



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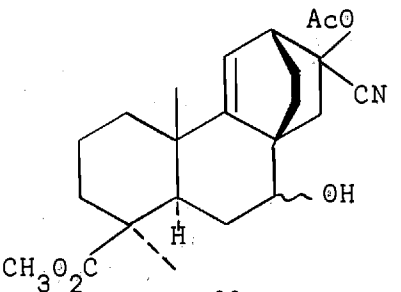
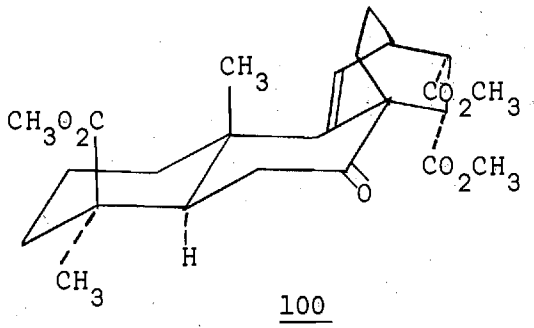


99

With the lack of success in the use of other dienophiles, attention was returned to the utilization of adducts 90 and 91 in the synthetic sequence. Accordingly, esterification of adducts 90 and 91 with diazomethane in ether gave a mixture of triesters 100 and 101. Separation was achieved by chromatography on acid-washed alumina. The first

adduct eluted with benzene was triester 100, in approximately 25 per cent yield, as a white crystalline solid, m.p. 151-153°C. The infrared spectrum of 100 showed absorptions at 1740 cm^{-1}, 1735 cm^{-1}, 1720 cm^{-1} (the three carboxylic esters), 1690 cm^{-1} (ketone), and 1620 cm^{-1} (double bond). The NMR spectrum of 100 gave two singlets for the tertiary methyl groups (δ0.98, 1.24), three singlets for the methoxy groups (δ 3.46, 3.51, 3.60), and a doublet (J = 7 cps) for the vinyl proton (δ 5.89). The mass spectrum gave a parent ion at M^+ = 432 (calcd. for



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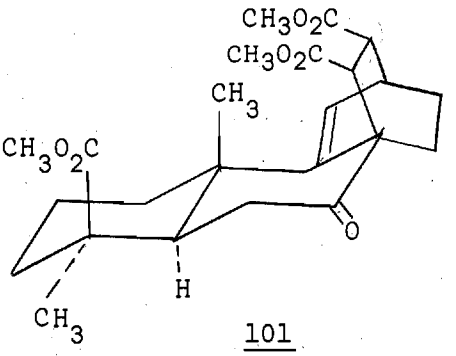


101

$C_{24}H_{32}O_7$; M^+ = 432). The infrared spectrum of 101 gave absorptions at 1745, 1730, 1710 cm^{-1} for the three carboxylic esters, 1700 cm^{-1} for the ketone, and 1620 cm^{-1} for the double bond. The NMR spectrum of 101 showed two singlets for the tertiary methyl groups (δ 1.10, 1.19), three singlets for the methoxy groups (δ 3.44, 3.48, 3.61), and a doublet (J = 7 cps) for the vinyl proton (δ 5.80). The mass spectrum gave a parent ion at M^+ = 432 (calcd. for $C_{24}H_{32}O_7$; M^+ = 432).

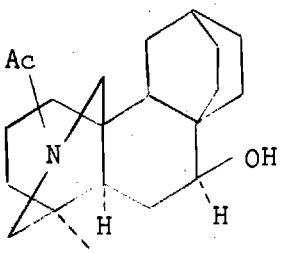
The following facts suggested the structural assignments for the adducts. As stated previously, the NMR spectrum of the mixture of adducts 90 and 91 gave absorptions for tertiary methyl groups at δ 0.85, 0.98, 1.21, and 1.25 while the NMR spectrum of triester 100

gave absorptions for tertiary methyl groups at δ 0.98 and δ 1.25. The absorptions for triester 100 corresponded to the absorptions at δ 0.98 and δ 1.25 in the mixture of adducts 90 and 91. Since the position of absorption of the methyl groups of triester 100 has not changed in the NMR spectrum compared to the parent anhydride, the bridge containing the ester groups must be on the (α) face of the molecule and consequently have the structure assigned. The methyl groups of triester 101 gave absorptions in the NMR spectrum at δ 1.10 and δ 1.19. The methyl group which absorps at δ 1.19 is in the same environment as it was in the anhydride (δ 1.21). However, the absorption for the C-10 methyl group has shifted downfield from δ 0.85 to δ 1.10. This indicated that the C-10 methyl group was deshielded due to the close proximity of the ester groups. Thus the diester bridge must have the (β) configuration as assigned.

Additional evidence is the fact that 100 is eluted first on the alumina column. All of the polar groups in triester 101 reside on the same face (β) of the molecule and this leads to stronger absorption on alumina than is the case with triester 100 where there are polar groups on both the (α) and (β) faces of the molecule. This explanation has been suggested previously by Pelletier[2] for the difference in absorption of epimeric atisine (3) derivatives on alumina.

Although triester 101 could not be utilized for the synthesis of ajaconine (1) or atidine (2), it was used by Nabors[46] in the synthesis of a degradation product, 102, of ajaconine (1). This synthesis of 102 provided the first synthetic evidence for the location of the oxygen

function in ring-B at C-7. The position of the oxygen functionality had been previously based entirely on spectral evidence.



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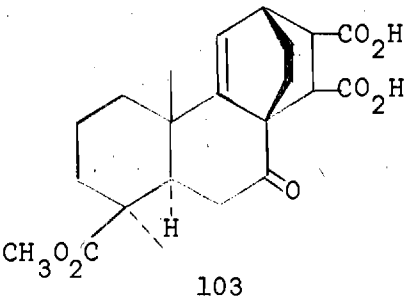

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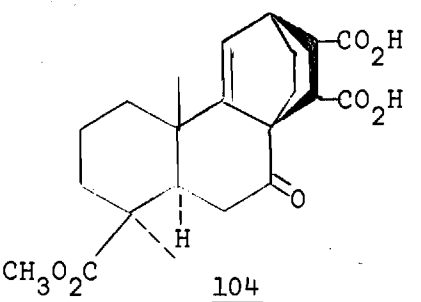
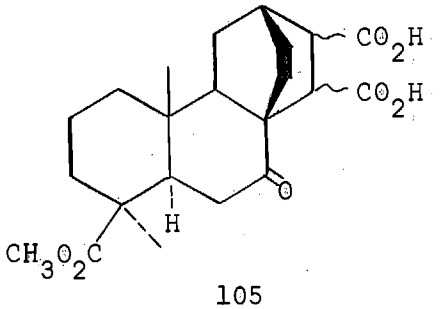


104

Saponification of triester 100 with aqueous sodium hydroxide in methanol gave diacid 103 as a white glassy material which resisted all crystallization attempts. The structure was partially confirmed by absorptions in the infrared spectrum for a carboxylic acid (3500-2400 cm^{-1}, 1710 cm^{-1}), a carboxylic ester (1725 cm^{-1}), a ketone (1710 cm^{-1}), and a double bond (1610 cm^{-1}). The NMR spectrum of 103 gave two singlets for tertiary methyl groups (δ 0.99, 1.20), a singlet for the methoxy group (δ 3.69), a doublet (J = 7 cps) for the vinyl proton (δ 6.25), and a broad singlet for the two acid protons (δ 11.3). The mass spectrum gave the parent ion at M^+ = 404 (calcd. for $C_{22}H_{28}O_7$; M^+ = 404).

Diacid 103 was hydrogenated to yield diacid 105 with the hydrogen being absorbed from the less hindered (α) face. That hydrogen was absorbed from the (α) face is shown by correlation of diacid 105 with known compound 109 [40] as illustrated in Figure 5. The (α) face is the less hindered side because it is opposite the C-10 methyl group. Hydrogenation of 105 was in sharp contrast to diacid 104 which resisted

hydrogenation.[47] It has been suggested, in analogy to the results reported on similar compounds,[40] that the observed resistance of 104 to hydrogenation results from the fact that all of the polar groups reside on the same (β) face of the molecule. This leads to adsorption on the catalyst surface of the (β) side, the side remote from the double bond. This provides additional confirmation for the structure assigned to adducts 100 and 101. The infrared spectrum of 105 gave absorptions for an acid (3500-2400 cm^{-1}), an ester (1725 cm^{-1}), and a ketone (1705 cm^{-1}). The NMR spectrum gave resonance signals at δ 0.84 and δ 1.22 for the two tertiary methyl groups, δ 3.68 for the methoxy group, and δ 10.03 for the two acid protons. The mass spectrum gave a parent ion at M^+ = 406 (calcd. for $C_{22}H_{30}O_7$; M^+ = 406).



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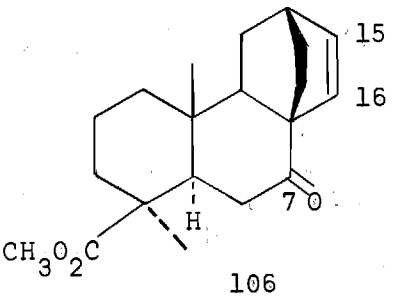


106

Bis-decarboxylation of diacid 105 with lead tetraacetate in pyridine gave keto-ester 106 in approximately 30 per cent yield. The yields varied greatly when this reaction was repeated. The NMR spectrum of 106 showed two methyl singlets centered at δ 1.00 and δ 1.18, respectively, a methoxy singlet at δ 3.68, a one proton doublet of doublets (J = 7 cps) centered at δ 6.17, and a one proton doublet (J = 7 cps) centered at δ 7.00. The doublet at δ 7.00 can be easily

assigned to C-16 since it is adjacent to only one proton (thus giving a doublet) and absorps at a low field position. The low field position is due to deshielding by the C-7 carbonyl group. The infrared spectrum of 106 showed absorptions at 1725 cm^{-1} for an ester, 1695 cm^{-1} for a ketone, and 1600 cm^{-1} for a double bond.

Correlation of triester 100 with known compound 68 [40] was provided by the sequence of reactions depicted in Figure 4. This correlation provided uncontestable evidence for the total structure of triester

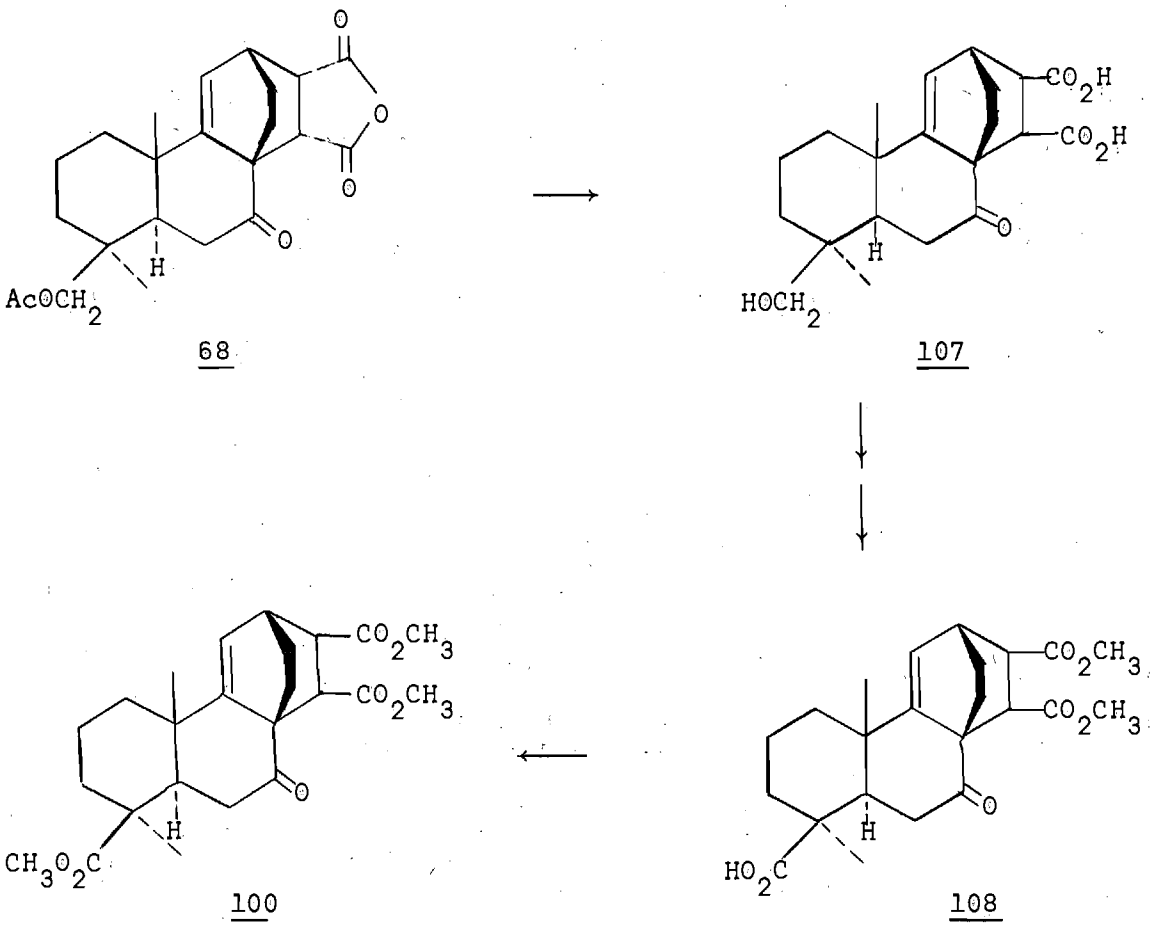
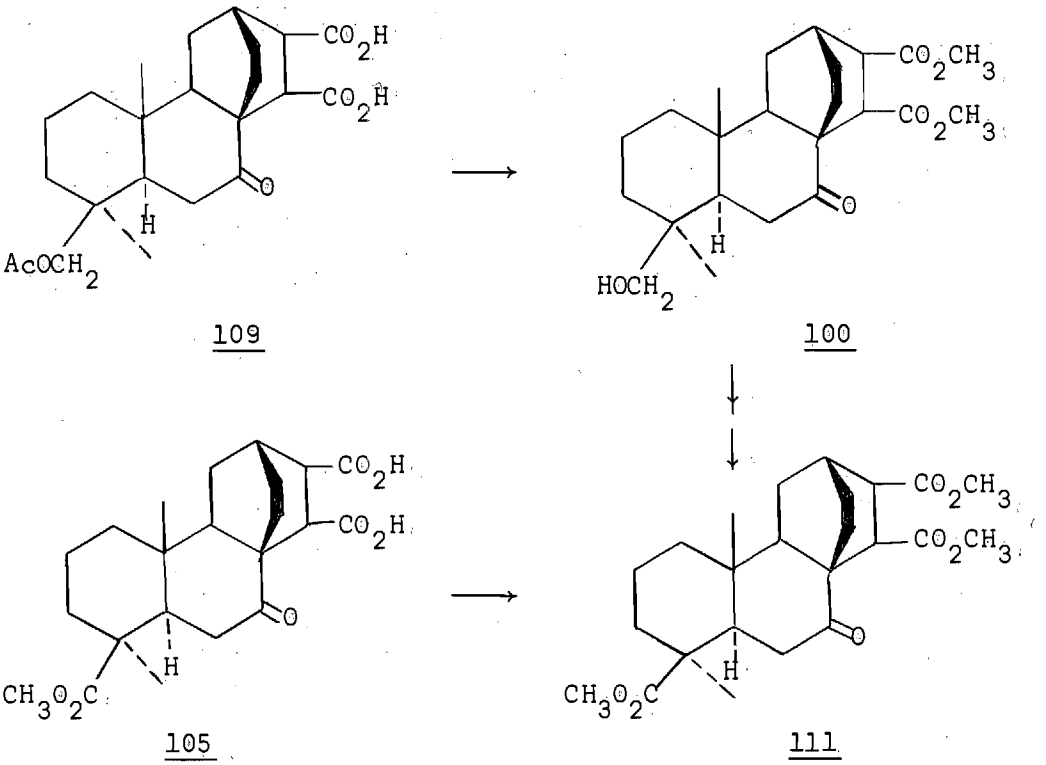


Figure 4. Correlation of Compound 100 with Known Compound 68

100, and thence 106, since compound 68 had been correlated with known compound 57 [40] which had, in turn, been converted[28] to hydrocarbon (+)60. The correlation was performed by saponification of anhydride 68 in aqueous sodium carbonate-methanol solution to give diacid-alcohol 107 which was esterified with diazomethane and oxidized with chromic anhydride in pyridine to give compound 108. Esterification of 108 with diazomethane gave a non-crystalline product. GLC analysis (mixed injections) showed that the retention time (3.3 min) of this product was identical to the retention time exhibited by triester 100. Also, the infrared and NMR spectra of this product were identical to the corresponding spectra of authentic triester 100.

Diacid 105 and known[40] compound 109 were correlated through the conversion of both compounds to triester 111 as depicted in Figure 5.



109 100

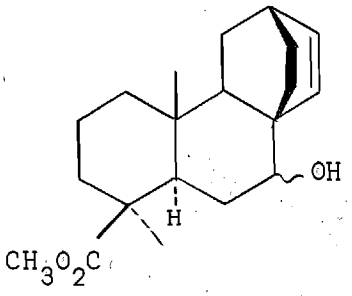
105 111

Figure 5. Correlation of Diacid 105 with Known Compound 109

Compound 109 was converted to triester 111 by saponification with sodium hydroxide, esterification with diazomethane, oxidation with Kilani's reagent, and esterification again. Crystalline compound 111, m.p. 142-144°C, showed absorptions in the infrared spectrum at 1735 cm^{-1}, 1725 cm^{-1}, 1715 cm^{-1} for the three carboxylic esters groups, 1685 cm^{-1} for the ketone, and 1625 cm^{-1} for the double bond. The NMR spectrum showed two singlets (δ 0.92, 1.20) for the tertiary methyl groups and three singlets (δ 3.63, 3.67, 3.74) for the three methoxy groups. The mass spectrum gave a parent ion at M^+ = 434 (calcd. for $C_{24}H_{34}O_7$; M^+ = 434). These properties were identical to those obtained upon esterification of compound 105. Similar correlations[47] performed with triester 101 supported the assigned structure.

Since the structure of 106 had been established unequivocally, efforts were then concentrated on the functionalization of the C/D ring system in compound 106. The approach envisaged was formation of a C-15 ketone and subsequent transformation to an *exo*-cyclic methylene group by a Wittig reaction.[48] The C/D ring system containing the C-15 *exo*-cyclic double bond would then be convertible to the C/D ring system of ajaconine (1) by procedures described by Ireland and co-workers.[27] In order to retain the oxygen functionality at C-7, compound 106 was converted to acetate 113 by sodium borohydride reduction, to give intermediate alcohol 112, and acetylation with acetic anhydride in pyridine. The infrared spectrum of 113 showed absorptions at 1725 cm^{-1} for the esters, 1610 cm^{-1} for the double bond, and 1240 cm^{-1} for the acetate group. The NMR spectrum showed two singlets for the tertiary methyl groups (δ 0.84, 1.20), one singlet for the acetate group (δ 2.02), one

singlet for the methoxy group (δ 3.65), and a doublet (J = 3 cps) for the two vinyl protons centered at δ 6.13. It is interesting that the C-15,16 protons, which had shown two multiplets in 106, now show only one multiplet in the absence of the deshielding effect of the ketone. The GLC-MS gave a parent ion at M^+ = 360 (calcd. for $C_{22}H_{32}O_4$; M^+ = 360).



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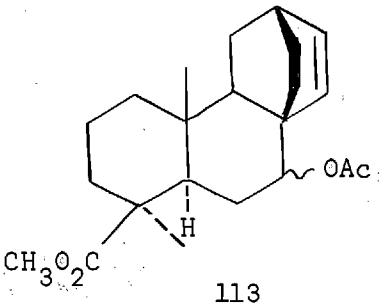
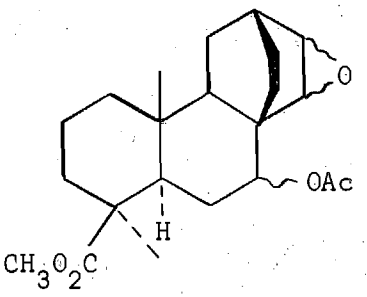


113

Hydroboration of 113 was attempted using two procedures described by Brown and co-workers.[49,50] The first procedure involved *in situ* formation and reaction of the borane derivative of 2-methyl-2-butene with compound 113. It was thought that the bulky alkyl borane derivative might help direct functionalization of the desired C-15 position. The second procedure involved external formation of diborane which was then bubbled into a solution of 113 in THF. In order to eliminate the possibility of epimeric alcohols, the crude products were treated with chromic anhydride in pyridine. GLC analysis of the products showed them to be extremely complex mixtures containing over eight major components. Because of the complexity of the reaction mixtures no further attempts to hydroborate 113 were executed.

An attempt was made to obtain a C-15 ketone by epoxidation of 113 and subsequent acid rearrangement. When compound 113 was treated with

m-chloroperbenzoic acid, in dry ether, epoxide 114 was obtained. GLC analysis showed the product to be a mixture of two epimers with R_t 7.4 min. (60%) and 8.0 (40%). The infrared spectrum of 114 showed absorptions at 1725 cm^{-1} for the esters and at 1240 cm^{-1} for the acetate group. The NMR spectrum of 114 showed absorptions at δ 1.20 and δ 1.26 for the two tertiary methyl groups, δ 2.02 for the acetate group, and δ 3.68 for the methoxy group. The mass spectrum gave a parent ion at M^+ = 376 (calcd. for $C_{22}H_{32}O_5$; M^+ = 376). Rearrangement of epoxide 114 was attempted by treatment with boron trifluoride-etherate in dry benzene. Isolation of ketonic material was attempted using Girard's "T" reagent. This attempt resulted in the isolation of only a trace of material which could not be characterized.



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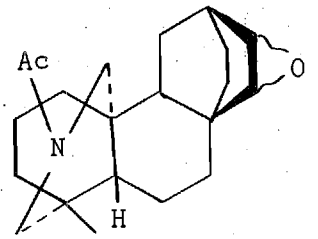

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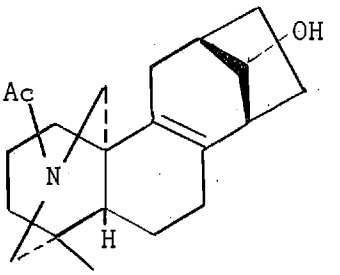
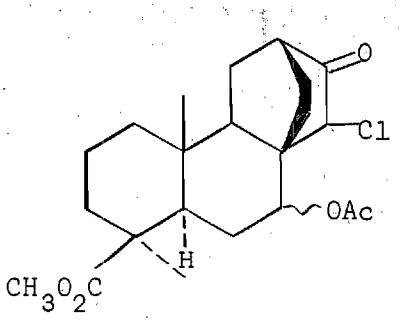


116

It was thought that rearrangement of epoxide 114, similar to that reported by Pelletier[51] when epoxide 115 gave 116, might have occurred.

Treatment of 113 with nitrosyl chloride and subsequent acid hydrolysis could conceivably provide compound 117 containing a C-15 ketone. When nitrosyl chloride was added to 113 in chloroform at -60°C and then hydrolyzed in concentrated hydrochloric acid as described by Meinwald,[52] only starting material was recovered. Treatment of 113

with nitrosyl chloride at 0°C and subsequent hydrolysis gave a complex mixture showing ten major components according to GLC analysis. Chromatography failed to achieve further purification. Because of the lack of success in obtaining a fairly clean reaction this route was not pursued further.

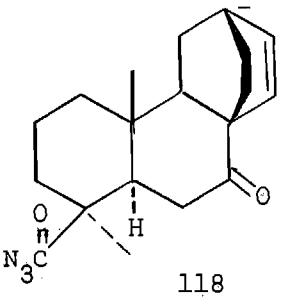


117

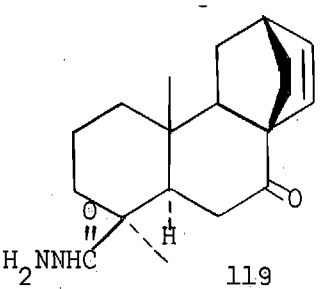
Efforts were then directed toward formation of the nitrogen containing E-ring of ajaconine. It was thought that this would be accomplished by photolysis of azide 118 which would be synthesized *via* hydrazide 119. Formation of hydrazide 119, directly from 106, was attempted by refluxing 106 in hydrazine hydrate using a procedure described by Smith.[53] However, all attempts were unsuccessful as evidenced by recovery of material still containing the carboxylic ester. The recovered material showed no absorptions in the NMR spectrum which could be assigned to vinyl protons. It was thought that this was due to the formation of the well-known hydrogenating reagent, diimide. Formation of diimide by refluxing hydrazine in air has been reported as a standard synthetic procedure.[54]

The next sequence of reactions involved attempted formation of hydrazide 119 in a manner described by ApSimon and Edwards.[14] Compound

113 was saponified in diethylene glycol and sodium hydroxide solution at 165-170°C to give crystalline acid alcohol 120, m.p. 218-220°C. The infrared spectrum of 120 gave absorptions for an acid (3600-2400 cm^{-1}, 1690 cm^{-1}), an alcohol (3450 cm^{-1}), and a double bond (1625 cm^{-1}). The NMR spectrum gave two singlets (δ 0.95, 1.28) for the tertiary methyl

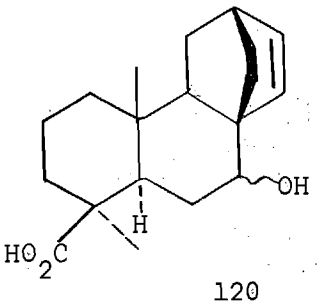


118

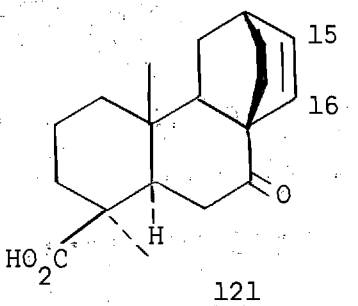


119

groups and a broad singlet (δ 6.33) for the two vinyl protons. The mass spectrum gave a parent peak at M^+ = 304 (calcd. for $C_{19}H_{28}O_3$; M^+ = 304). Oxidation of 120 with Jones reagent gave crystalline keto-acid 121, m.p. 182-184°C. The infrared spectrum of 121 gave absorptions



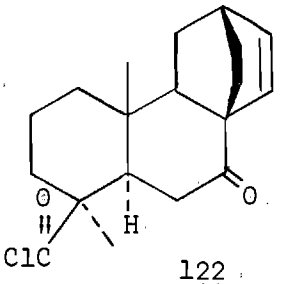
120



121

for an acid (3600-2400 cm^{-1}, 1690 cm^{-1}), a ketone (1725 cm^{-1}), and a double bond (1600 cm^{-1}). The NMR spectrum showed two singlets (δ 1.15, 1.25) for the tertiary methyl groups, a doublet of doublets (δ 6.17, J = 8 cps) for C-15 proton, and a doublet (δ 6.80, J = 8 cps) for the

C-16 proton. The mass spectrum gave a parent ion at M^+ = 302 (calcd. for $C_{19}H_{26}O_3$; M^+ = 302). Reaction of 121 with thionyl chloride in pyridine gave crystalline acid chloride 122, m.p. 107-110°C. Compound 122 gave absorptions in the infrared spectrum for an acyl chloride (1780 cm^{-1}), a ketone (1700 cm^{-1}), and a double bond (1600 cm^{-1}). When acid chloride 122 was treated with hydrazine in benzene the desired product, hydrazide 119, could not be isolated. Reaction of hydrazine with the C-7 ketone in some fashion might explain the complex mixture of products.



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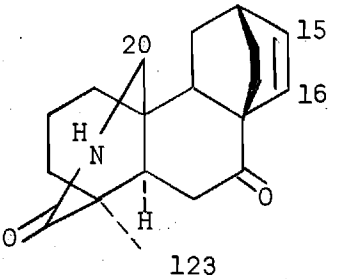


123

While attempting to find an alternate approach for the formation of azide 118, Nabors[47] found that one could react the acid chloride derivative of podocarpic acid[53] with sodium azide in dioxane to give quantitative yields of the azide. When compound 122 was reacted with sodium azide in this fashion, azide 118 was obtained in excellent yield. The infrared spectrum showed absorption for an azide (2120 cm^{-1}) and a ketone (1685 cm^{-1}). An attempt was made to convert azide 118 to lactam 123 by photolysis in hexane solution with a Hanovia 400 watt ultraviolet lamp. The photolytic reaction was to be carried out at 0°C. However, the temperature in the cell rose to approximately 40°C after the lamp had been turned on for 20 minutes. When an attempt was

made to isolate the products from this reaction, only a trace of a non-crystalline compound, which appeared to be lactam 123, was obtained. The infrared spectrum showed absorptions for a lactam (1650 cm^{-1}) and a ketone (1700 cm^{-1}). The GLC-MS gave a parent ion at M^+ = 299 (calcd. for $C_{19}H_{25}O_2N$; M^+ = 299). Not enough material was available to obtain a clear NMR spectrum. The NMR spectrum would be very characteristic since the desired isomer would show only one tertiary methyl group in contrast to the other two possible isomers which would show absorptions for two methyl groups. Since azides are known[55] to undergo thermal decomposition to isocyanates, the low yield was attributed to the high reaction temperature caused by the poorly designed photolysis cell which had only an external jacket for cooling.

Attention was again focused on an attempt to provide functionalization of the C/D ring system by reacting various dienophiles with dienes 89 and 98 under sealed tube conditions. GLC analysis indicated that all reactions attempted between α-acetoxyacrylonitrile and these dienes failed. Citraconic anhydride was then used as the dienophile with dienone 89 in a sealed tube at 150°C. That two adducts were obtained with R_t 4.8 minutes (20%) and 5.6 minutes (10%) was shown by GLC analysis (C.T. 270°C). The reaction was carried out at a variety of temperatures and times, as listed in Table 1, to find the optimum conditions. Unless otherwise indicated, all the reactions in Table 1 were carried out in a sealed tube with a ten-fold excess of citraconic anhydride. This study indicated that the optimum reaction conditions were at a temperature of 150°C for 48 hours. Since this is an equilibrium reaction, a large excess of citraconic anhydride gave slightly higher yields as indicated

Table 1. A Study of the Diels-Alder Reaction Between Dienone 89 and Citraconic Anhydride (93)

Temperature °C	Time	% 1st Adduct	% 2nd Adduct
125	48 Hours	6.43	3.09
125	96 Hours	9.12	4.47
125	10 Hours	19.2	11.1
142	50 Hours	18.5	3.1
142	4 Days	15.3	8.1
142	10 Days	19.0	8.7
150	3.5 Hours	-	-
150	24 Hours	10.6	5.8
150	48 Hours	20.6	10.0
150	64 Hours	18.7	10.5
150	48 Hours*	29.0	18.3
210	24 Hours	6.37	1.1
210	48 Hours	-	-

*110 Fold excess of 93.

in Table I. After obtaining the adducts an attempt was made to hydrogenate the mixture by using 5 per cent Pt/C as the catalyst and acetic acid as the solvent. The lack of disappearance of the vinyl proton in the NMR spectrum indicated that hydrogenation had not occurred.

The first adduct, m.p. 175-180°C (R_t 4.8 minutes) was obtained in approximately 85 per cent purity by repeated chromatography on silica gel. The infrared spectrum gave absorptions for an anhydride (1840 cm^{-1}, 1775 cm^{-1}), a carboxylic ester (1720 cm^{-1}), a ketone (1705 cm^{-1}), and a double bond (1625 cm^{-1}). The NMR spectrum gave absorptions for three tertiary methyl groups (δ 0.84, 1.20, 1.48), one methoxy group (δ 3.68), and a doublet (J = 7 cps) for the vinyl proton at δ 4.11. The mass spectrum gave a peak at M^+ = 400 (calcd. for $C_{23}H_{28}O_6$; M^+ = 400). An exact mass determination using $F(CF_2)_nF$ as

the standard gave M^+ = 400.2021 (known; M^+ = 400.1886). It was not possible to select the correct structure for the first adduct (R_t 4.8 min.) from the four possible ones (see Figure 6) with the available data.

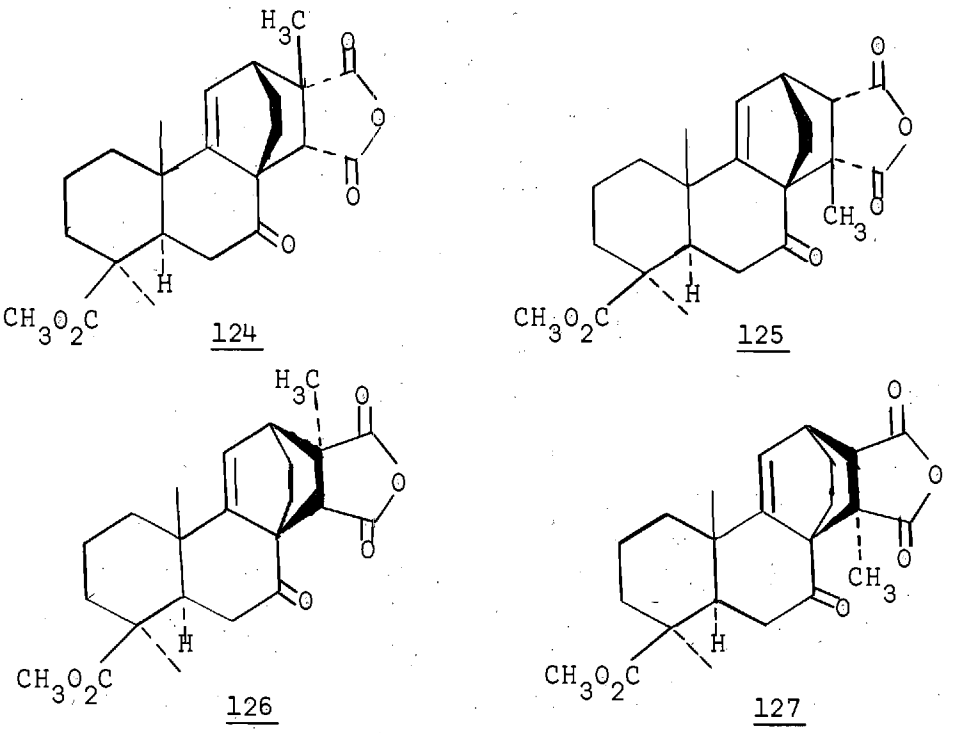


Figure 6. Possible Diels-Alder Adducts from the Reaction of Dienone 89 with Citraconic Anhydride (93)

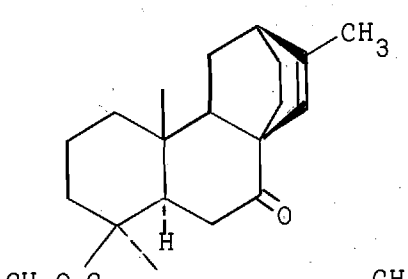
It was thought that if the first adduct (R_t 4.8 min) should be the desired adduct, 124, then intermediate 94 could be obtained by a sequence of reactions analogous to those performed on compound 90. Also the presence of a double bond at C-15,16 would give unequivocal evidence concerning the sterochemistry of the C/D ring system. A double bond on the (β) face would shift the C-10 methyl group to a high field position[56] (approximately δ 0.60); whereas a double bond on the (α) face would have no effect.

The first adduct (R_t 4.8 min) was converted into a triester, m.p. 92-95°C. The infrared spectrum of the triester gave absorptions for carboxylic ester groups (1730 cm^{-1}), a ketone (1690 cm^{-1}), and a double bond (1605 cm^{-1}). The NMR spectrum of the triester gave three singlets (δ 0.84, 1.18, 1.65) for the tertiary methyl groups, three singlets (δ 3.57, 3.59, 3.68) for the methoxy groups, and a doublet (δ 3.68, J = 8 cps) for the vinyl proton. The mass spectrum gave a parent ion at M^+ = 446 (calcd. for $C_{25}H_{34}O_7$; M^+ = 446). Saponification of the triester gave a crude product which showed absorptions in the infrared spectrum for an anhydride (1840, 1775 cm^{-1}), an acid (3600-2400, 1690 cm^{-1}), an ester (1710 cm^{-1}), and a double bond (1610 cm^{-1}). This indicates that a large amount of the diacid formed was converted to the anhydride when the basic solution was acidified. Hydrogenation of the crude saponification product was attempted under a variety of conditions. That only 30 per cent of the material underwent hydrogenation was shown by integration of the vinyl proton region in the NMR spectrum.

The crude hydrogenation mixture was treated with lead tetraacetate in pyridine. Repeated chromatography of the mixture yielded only a small amount of a compound which showed only one peak with R_t 1.4 min according to GLC analysis (C.T. 270°C). Not enough material was available to obtain a clear NMR spectrum. However, there was a sharp singlet at δ 0.68 which showed that the double bond was on the (β) face of the molecule. This indicated that this material must be either compound 128 or 129 and, consequently, the first adduct (R_t 4.8 min) must have structure 126 or 127. The available data does

not allow one to locate the position of the tertiary methyl group in the C/D ring system. Thus one cannot distinguish between structures 126 and 127 for the first adduct (R_t 4.8 min). The second adduct has not been isolated in sufficient purity to allow determination of its structure.

It was thought that decarboxylation of the diacid obtained by saponification of the first adduct (R_t 4.8 min) could give additional structure evidence by providing diene 130. However, when the basic solution was acidified, the majority of the material was converted to the starting anhydride. Decarboxylation was attempted on this material, but only starting material, and a compound which showed bands in the infrared spectrum at 1725 cm^{-1}, 1675 cm^{-1}, and 1600 cm^{-1}, was obtained.



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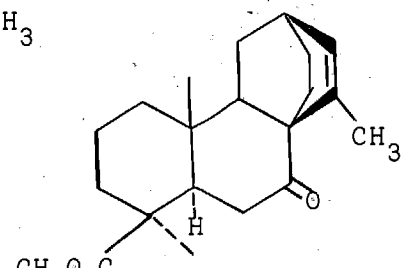

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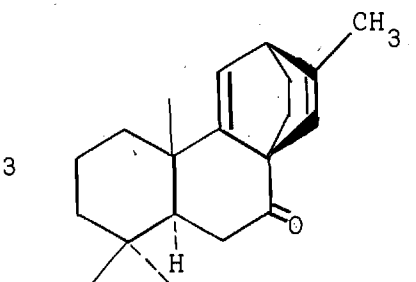

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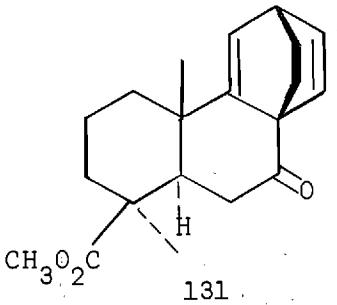
It was thought the citraconic anhydride adducts might be hydrogenated if extremely high pressures were used. Hydrogenation was attempted with Raney nickel in basic solution at 1400 p.s.i. and room temperature without success. Hydrogenation attempts with 5 per cent Pt/C in acetic acid at 1400 p.s.i. and 100°C also failed.

Because of the difficulties encountered in structure elucidation and hydrogenation, and lack of time, no further work was carried out with the citraconic anhydride adducts.

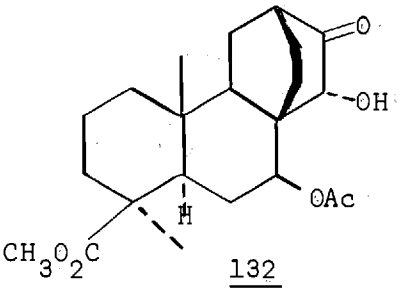
Since decarboxylation of compound 105 had always given poor yields (30 per cent or less), it was decided to attempt decarboxylation under electrolysis conditions recently reported by van Tamelen[57] and Dauben[58] to give a good yield (60 per cent) of decarboxylated product.

When compound 103 was electrolyzed in pyridine, triethylamine, and at approximately 100 volts (0.5-0.8 amp) with platinum electrodes, a crystalline diene 131, m.p. 86-87°C, was obtained in poor yield (< 5 per cent). The infrared spectrum gave absorptions for an ester (1720 cm^{-1}), a ketone (1690 cm^{-1}), and a diene system (1630 cm^{-1}). The NMR spectrum gave singlets (δ 0.93, 1.21) for the two tertiary methyl groups, a singlet (δ 3.69) for the methoxy group, and a multiplet centered at δ 4.20 for the three vinyl protons. The mass spectrum gave the parent ion at M^+ = 314 (calcd. for $C_{20}H_{26}O_3$; M^+ = 314). Another compound, m.p. 172-174°C, was isolated which showed absorptions in the infrared spectrum at 1780 cm^{-1} (possibly a lactone) and 1710 cm^{-1} (ester). The NMR spectrum gave signals for two tertiary methyl groups (δ 1.15, 1.18), and one methoxy group (δ 3.70). The mass spectrum failed to give a recognizable parent ion. A structure could not be assigned to this compound.

A new approach to functionalization of the C/D ring system in compound 113 was proposed. It concerned rearrangement of epoxide 114 in DMSO using procedures described by Tsuji[59] to hopefully give 132 as the major product. A successful Wittig reaction would give the desired



131



132

C/D ring system contained in ajaconine. With this in mind, epoxide 114 was stirred in DMSO at 100°C for 30 hours while air was being bubbled through the solution. GLC analysis (C.T. 240°C) showed the presence of three new components with R_t 3.2 min (32%), 3.6 min (11%), and 3.9 min (8%). GLC-MS analysis of the component at R_t 3.2 min gave an ion at M^+ = 392 (calcd. for $C_{22}H_{32}O_6$; M^+ = 392). No further data was obtained on this reaction at this point. Since partial evidence indicated that the C/D ring could possibly be functionalized in three steps from a compound containing a C-15,16 double bond, attention was focused on the production of the nitrogen containing E-ring since all attempts had been unsuccessful.

The synthesis of lactam 123 was achieved by photolysis of azide 118 obtained in the manner previously described in this thesis. A newly designed photolysis cell which had a cooling jacket between the Hanovia 400 watt ultraviolet lamp and the solution was responsible for the good yield (20%) of crystalline lactam 123, m.p. 253-255°C. The cell also had an external jacket, which when connected with the internal jacket and a cooling unit, maintained the reaction temperature at 0°C. The infrared spectrum of 123 showed absorptions for a ketone

(1700 cm^{-1}), a lactam (1650 cm^{-1}), a double bond (1600 cm^{-1}), and for protons on nitrogen (3200 cm^{-1}). The NMR spectrum showed one singlet for a tertiary methyl group (δ 1.17), a doublet of doublets (J = 13 cps) centered at δ 3.68 for the C-20 protons, a doublet of doublets (J = 8 cps) centered at δ 6.26 for the C-15 proton, and a doublet (J = 8 cps) centered at δ 6.98 for the C-16 proton. The mass spectrum gave a parent ion at M^+ = 299 (calcd. for $C_{19}H_{25}O_2N$; M^+ = 299). Precise mass determination using 1,2-dichlorooctafluorocyclohexene-1 as the standard gave the parent ion at M^+ = 299.1860 (calcd. M^+ = 299.1885).

Some comments should be made at this point concerning the ORD of some of the ketones prepared in the course of this study.

All tetracarbocyclic ketones (105, 106, 111, 121, 123) containing a saturated B-ring demonstrated negative Cotton effects. Application of the octant rule to these compounds, in a manner described by Crabbe,[60] predicts a negative Cotton effect when the B-ring is in a chair conformation and a positive Cotton effect for the boat conformation. Consequently, the B-ring of all of these compounds must be in the chair conformation.

The B-ring of compounds 100 and 103 forms part of a β,γ-unsaturated cyclohexanone system. It has been shown[61] that such systems can show intense UV absorptions and very strong Cotton effects when the geometry is suitable. However, the Cotton effects are best interpreted in terms of the octant rule for a saturated system when the carbonyl and ethylenic linkages cannot interact appropriately.[62] Because of this lack of interaction, the properties are more characteristic of a saturated system. The fact that the Cotton effects of

unsaturated compounds 100 and 103 are of the same order of magnitude as for the analogous saturated compounds indicates that the octant rule can be applied to these compounds. The octant rule would predict a negative Cotton effect for compounds 100 and 103 when the B-ring occupies the half-chair conformation and a positive Cotton effect when it is in the boat form. Since compounds 100 and 103 show a negative Cotton effect (see Table 2), the B-ring of these must be in the half-

Table 2. ORD of Some Tetracarbocyclic Ketones

Compound	Wave Length (mμ) at [Φ]	α
100	292	-134
101	289	+ 48
103	285	-101
105	294	- 53
106	299	- 95
111	299	- 86
121	294	- 89
123	292	- 88
131	297	- 33

chair form. This is direct contrast to unsaturated ketone 101 (see Table 2), and compounds prepared from 101 by Nabors,[47] which contained bulky groups at C-13,14. Since these compounds demonstrated a positive Cotton effect, their B-rings must be in the boat conformation. The existence of these compounds in the boat form was rationalized[47] in light of the interactions involved between the C-4 carboxyl group and the methylene group at C-16. Therefore the existence of compounds 100 and 103 in the half-chair form appears to be anomalous and could be due

to a strong interaction in the boat form of the bulky CO_2R group at C-16 with the methylene group at C-6 as shown in Figure 7.

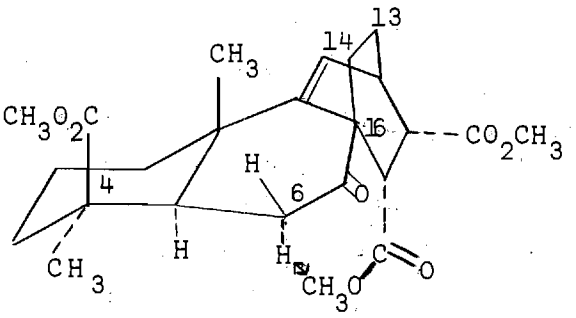


Figure 7. Interaction of the Ester Group at C-16 with the Methylene Group at C-6 in Compound 100

When there is no bulky group at C-16 the boat conformation is preferred probably because it eliminates a bad diaxial interaction present in the half-chair conformer between the hydrogen at C-6 and the CO_2R group at C-4.

Compound 131 has a B-ring which forms part of a $\beta,\gamma,\beta',\gamma'$-unsaturated system. Since this compound shows a weak Cotton effect it could possibly be treated as a saturated system with application of the octant rule showing compound 131 to be in a half-chair conformer. Further work on these systems is needed for a comprehensive interpretation of the Cotton effect of this compound.

CHAPTER III

INSTRUMENTATION AND EQUIPMENT

Spectral Studies

Nuclear magnetic resonance spectra were obtained using a Varian Associates Model A-60A spectrometer equipped with a spin-decoupler. Tetramethylsilane was used as an internal standard. The abbreviations, b.s., s, d, t, q, and m refer to broad signal, singlet, doublet, triplet, quartet, and multiplet, respectively.

Mass spectral data were obtained using a Varian Associates Model 66 mass spectrometer,* or a Varian Associates Model 66 mass spectrometer equipped with a Series 200 gas chromatograph* and a Model V-5500 GC/MS interface.

Infrared spectra were obtained using a Perkin-Elmer Model 237B spectrophotometer. The spectra of liquids were taken as films formed between two sodium chloride plates; potassium bromide was used in preparing pellets of solid samples for infrared spectra. The band at 1601 cm^{-1} of a polystyrene film (0.05mm) was used as a reference point.

The optical rotary dispersion, circular dichroism, and ultraviolet spectra were obtained with a Jasco Model ORD/UV-5 spectrophotometer.

The optical rotations were determined using a Rudolph polarimeter

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*These spectra were run by Mr. G. Turner.

equipped with a General Electric Sodium Lab-Arc lamp as the source of the sodium D line.

Physical Separations

Gas-liquid chromatography (GLC) was performed using a F & M Model 400 Biomedical gas chromatograph with a hydrogen flame detector. Glass columns (6' x 1/4" outside diameter) bent in a U shape were used with the F & M gas chromatograph. Glass columns (6' x 1/4" outside diameter) bent in a circular shape were used with the Varian Associates gas-liquid chromatograph-mass spectrometer. The column temperature (C.T.), helium flow rate (H.F.R.), and the retention time (R_t) are given in the experimental section for each example. Gas-Chrom-Q (GCQ) was used as solid support unless otherwise stated. Gas-Chrom-Q is defined by the Applied Science Laboratories catalog as Gas-Chrom-P (made from Eagle-Picher Celatom) treated with dimethyldichlorosilane. The relative peak areas were measured using a Gelman Instruments Company planimeter or by accurately cutting out the peaks and weighing them on an analytical balance. The column substrates and solid supports used in the GLC analyses were obtained from Applied Science Laboratories or from Hewlett Packard Analytical Instruments.

Thin layer chromatography (TLC) was performed using silica gel or neutral alumina coated microscopic slides.

Miscellaneous

Melting points are uncorrected and were taken on a Thomas-Hoover capillary melting point apparatus or a Koffler melting point apparatus.

Analyses were performed by Alfred Bernhardt Microanalytical Laboratories, Mulheim, West Germany.

CHAPTER IV

EXPERIMENTAL

Attempted Preparation of the E and F Rings of Ajaconine (1) using a Model System

Attempted Hydrogenation of 69

Anhydride 69, (5 g)[40], was dissolved in acetic acid (400 ml). After addition of 5 per cent Pt/C (0.7 g), the solution was allowed to react with an excess of hydrogen at room temperature and atmospheric pressure for eight days. The catalyst was removed by filtration and the solvent was evaporated *in vacuo* to yield 5 g of a white crystalline solid. The m.p., 266-267°C,[40] as well as the infrared spectrum was identical to that of the starting material 69.

The anhydride 69, (4.37 g)[40] was dissolved in ethyl acetate (250 ml). After addition of 5 per cent Pt/C (1.5 g), the solution was allowed to react with an excess of hydrogen at room temperature and atmospheric pressure for one week. The catalyst was removed by filtration and the solvent was evaporated *in vacuo* to yield 4.30 g of a white crystalline solid. The m.p., 266-267°C[40] and infrared spectrum showed this material to be identical with anhydride 69.

Treatment of Anhydride 69 with Diazomethane: Preparation of Diester 75

The anhydride (69, 5 g) was dissolved in methanol (400 ml) and diazomethane (5 g) in ether was added until a yellow color persisted. After the excess diazomethane was allowed to evaporate slowly, the

solvent was removed *in vacuo* to yield 5.0 g of 75 as a yellow syrup, which resisted all attempts at crystallization. The infrared spectrum showed: ν_{max}^{film} 1740 cm^{-1} (CO_2Me), 1700 cm^{-1} (C = O), and 1625 cm^{-1} (C = C). The NMR ($CDCl_3$) spectrum of 75 showed signals at δ 1.28 (3H, S, C-CH_3), 1.51 (3H, S, C-CH_3), 2.20 (3H, S, COCH_3) and 5.68 (1H, d, C = CH, J = 7 cps).

Saponification of diester 75: Preparation of Diacid 76

Diester 75 (9.93 g) was suspended in a solution of 20 per cent sodium hydroxide (75 ml) and methanol (85 ml). After the solution had been refluxed for 18 hours, it was acidified with 6N hydrochloric acid, and extracted with ether. The organic layer was washed with water, dried over anhydrous magnesium sulfate, and evaporated *in vacuo* to give 8.34 g of 76 as a white glassy solid which resisted all crystallization attempts. The infrared spectrum (film) showed absorptions at 3450 cm^{-1} (alcohol), 1700 cm^{-1} (CO_2H), and 1650 cm^{-1} (C = C). The NMR (deuteroacetone) showed signals at δ 0.89 (3H, S, C-CH_3), 1.08 (3H, S, C-CH_3), 4.88 (b.s., OH), 5.65 (d, C=CH, J = 7 cps).

Attempted Hydrogenations of Diacid 76

Diacid 76 (4.55 g) was dissolved in acetic acid (150 ml) which was followed by addition of 5 per cent Pt/C (1.0 g). The mixture was allowed to react with an excess of hydrogen at room temperature and atmospheric pressure for six days. After the catalyst was removed by filtration, evaporation *in vacuo* yielded 4.34 g of a white glassy material which resisted all crystallization attempts. The infrared spectrum showed: ν_{max}^{film} 3400 cm^{-1} (acid-alcohol), 1690 cm^{-1} (COOH and C=O), and 1640 cm^{-1} (C=C). The tetranitromethane test for

unsaturation was run as follows: To a 0.5 mm layer of the product in a melting point capillary there was introduced a 5 mm column of tetranitromethane which introduced a yellow color typical of unsaturation.

The unsaturated diacid 76 (3.68 g) was again dissolved in acetic acid (100 ml) which was followed by addition of 5 per cent Pt/C (0.7 g). After the solution was allowed to stir in an excess of hydrogen at room temperature and atmospheric pressure for two hours, the catalyst was removed by filtration. After fresh 5 per cent Pt/C (0.7 g) had been added, the solution was allowed to react with hydrogen at atmospheric pressure and room temperature for 24 hours. No appreciable uptake of hydrogen was observed.

Preparation of Diels-Alder Adducts 90 and 91

Methylation of Podocarpic Acid* 53: Preparation of Methyl-O-Methyl Podocarpate 80

To podocarpic acid (53, 500 g) in a three liter beaker was added ice (500 g) along with methanol (500 ml) and sodium hydroxide (240 g). This mixture was stirred for two hours until a dark brown color persisted which was indicative of the formation of the phenoxy anion. After cooling the solution to 15°C in an ice bath, dimethylsulfate (425 ml) was added, dropwise, with stirring over a period of 1.5 hours until the reaction was completed as evidenced by solidification of the solution. A light brown solid was obtained by filtration of the solution after addition of one liter of water. This solid was stirred

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*The author is indebted to Dr. Ian K. Walker, Department of Scientific and Industrial Research, Wellington, New Zealand, for generous supplies of podocarpic acid.

into one liter of water and removed from the solution by filtration. Recrystallization from acetone yielded 455.4 g of methyl-o-methyl podocarpate (80), m.p. 127-128.5°C (reported[43] m.p. 128°C), as a white crystalline solid. The spectral properties of 80 were ν_{max}^{KBr} 1725 cm^{-1}, 1500 cm^{-1}, 1450 cm^{-1}; NMR ($CDCl_3$): δ 1.10 (3H, S, C-CH_3), 1.32 (3H, S, C-CH_3), 3.7 (3H, S, O-CH_3), 3.80 (3H, S, O-CH_3), 4.80 (3H, multiplet, aromatic).

Chromic Acid Oxidation of Methyl-O-methyl Podocarpate (80): Preparation of Methyl-O-methyl 7-Ketopodocarpate (62)

Methyl-O-methyl podocarpate (80, 1000 g) was oxidized with chromic acid to yield 724 g of ketone 62. This was done in ten 100 g runs. The following is a typical run: methyl-O-methyl podocarpate (100 g) was dissolved in one liter of acetic acid. Chromic acid (94 g) was dissolved in 800 ml HoAc/200 ml H_2O mixture which was then added to the ester solution at room temperature with stirring. After allowing the reaction mixture to stand overnight at room temperature, it was poured into a saturated aqueous sodium chloride solution. After allowing this solution to stand overnight, the precipitate was removed by filtration and washed with water to yield 72 g of ketone 62, m.p. 121-123°C (reported[41] 121-123°C), in the form of a yellow crystalline solid. The spectral properties of ketone 62 were ν_{max}^{KBr} 1725, 1675, 1600 cm^{-1}; NMR ($CDCl_3$): δ 1.26 (3H, S, C-CH_3), 1.07 (3H, S, C-CH_3), 3.86 (3H, S, O-CH_3), 3.68 (3H, S, O-CH_3), 6.66 (2H, multiplet, aromatic), 7.83 (1H, doublet, aromatic, J = 8 cps).

Sodium Borohydride Reduction of Methyl-O-methyl 7-ketopodocarpate (62): Preparation of Alcohol 81

Methyl-O-methyl 7-ketopodocarpate (62, 500 g) was dissolved in tetrahydrofuran (700 ml) and 95 per cent ethanol (1000 ml). After dissolving sodium borohydride (100 g) in water (400 ml) and 95 per cent ethanol (150 ml), this solution was added slowly to the keto-ester solution. This solution was stirred for 24 hours at room temperature, after which the salty-looking precipitate was removed by filtration. Evaporation of the solution *in vacuo* gave a pink syrup. The syrup was dissolved in ether (500 ml) and 5 per cent aqueous sodium chloride solution (500 ml) was added. The aqueous layer was extracted several times with 250 ml portions of ether. The ether extracts were combined, washed twice with 5 per cent aqueous sodium chloride (200 ml), dried over anhydrous magnesium sulfate and the solvent evaporated *in vacuo*. Crystallization from ether solution gave 443 g of alcohol 81, m.p. 100-106°C, in the form of a white crystalline solid. The infrared spectrum showed: ν_{max}^{KBr} 3500 cm^{-1}, 1715 cm^{-1}, 1610 cm^{-1}, 1575 cm^{-1}. The NMR spectrum ($CDCl_3$) showed signals at δ 0.87 (3H, S, C-C$\underline{H}_3$), 1.30 (3H, S, C-C$\underline{H}_3$), 3.70 (3H, S, O-C$\underline{H}_3$), 3.81 (3H, S, O-C$\underline{H}_3$), and 6.81 (3H, multiplet, aromatic). The position of the O$\underline{H}$ proton signal could not be determined. The mass spectrum showed the parent ion at M^+ = 318 (calcd. for $C_{19}H_{26}O_4$, M^+ = 318).

Anal. Calcd. for $C_{19}H_{26}O_4$: C, 71.76; H, 8.24

Found: C, 71.88; H, 8.35.

Birch Reduction and Dehydration of Alcohol 81: Preparation of Dienone 83

Compound 81 (440 g) was reacted in 11 runs, using 40 g of 81 in each run. The following procedure was used for each of the 11 reactions: To liquid ammonia (1000 ml) there was added 30 g of freshly-cut metallic sodium. A solution of ester-ol 81 (40 g) in tetrahydrofuran (100 ml) and absolute ethanol (10 ml) was added dropwise over a period of one hour. After allowing the solution to stir for one hour, addition of 50 per cent aqueous ethanol (120 ml) was required to discharge the dark blue color. After excess ammonia had been allowed to evaporate, the mixture was diluted with 5 per cent aqueous sodium chloride (200 ml) and extracted with three 125 ml portions of ether. The combined ether extracts were evaporated *in vacuo* to give a dark brown gummy material. This material was dissolved in 200 ml of methanol. Concentrated hydrochloric acid (10 ml) was added and the resulting solution was allowed to stand overnight at room temperature. The solvent was evaporated *in vacuo* and the residue taken up in ether (300 ml). The ether solution was washed four times with 5 per cent aqueous sodium chloride solution (30 ml), dried over anhydrous magnesium sulfate, and condensed *in vacuo* yielding 38 g of a reddish syrup. GLC analysis (10% SE-30 on 100/120 mesh GCQ column, C.T. 242°, H.F.R. 88 ml/min) of the material showed three peaks with R_t 1.1 min (15%), R_t 2.3 min (25%) and R_t 2.9 min (58%).

Separation of the mixture into a ketonic fraction was achieved by use of Girard's "T" reagent as follows: The reddish syrup (38 g) was dissolved in methanol (400 ml) and refluxed with 24.0 g of Girard's

"T" reagent for three hours. The methanol was evaporated *in vacuo* and the residue was diluted with three 100 ml portions of ether. The combined extracts were washed with water, dried over anhydrous magnesium sulfate, and labeled as non-ketonic fraction A.

The aqueous layer obtained from the above Girard's "T" separation was acidified with 60 ml of concentrated hydrochloric acid and allowed to stand on the steam bath for one hour. After cooling to room temperature, the aqueous layer was extracted with one 200 ml portion and two 150 ml portions of ether. The combined ether extracts were washed with four 50 ml portions of 5 per cent aqueous sodium chloride solution, dried over anhydrous magnesium sulphate, and labeled as the ketonic fraction B.

Fraction A (non-ketonic) yielded 10.74 g of a reddish syrup. The infrared spectrum showed: ν_{max}^{film} 3500-2500 cm^{-1} (carboxylic acid), 1700 cm^{-1} (acid carbonyl), 1600 cm^{-1} (double bond). GLC analysis (10 per cent SE-30 on 100/120 mesh GCQ column, C.T. 242°, H.F.R. 88 ml/min) of the material showed it to contain one major peak with R_t 1.0 min (66%) and one minor peak with R_t 2.3 min (33%).

Fraction B (ketonic) yielded 24.55 g of a reddish syrup. The infrared showed: ν_{max}^{film} 3500-2500 cm^{-1}, 1710 cm^{-1}, 1650 cm^{-1}, 1570 cm^{-1}. GLC analysis (10% SE-30 on 100/120 mesh GCQ column, C.T. 242°C, H.F.R. 88 ml/min) showed it to contain only one major component with R_t 2.6 min (89%). Total ketonic fraction obtained was 212.26 g in the form of a syrup. Crystallization from ether yielded approximately 110 g of crude dienone 83. Recrystallization from ether yielded pure 83, m.p. 200-202°C, of identical R_t and IR, in the form of a white crystalline

solid. The infrared (KBr pellet) spectrum gave absorptions at 3500-2500 cm^{-1} (carboxylic acid), 1700 cm^{-1} (acid carbonyl), 1640 cm^{-1} (α,β-unsaturated ketone), 1575 cm^{-1} (conjugated double bond). The NMR spectrum ($CDCl_3$) gave signals at δ 1.03 (3H, S, C-CH_3), 1.29 (3H, S, C-CH_3), 5.94 (1H, S, C=CH-C=O), 6.15 (1H, b.s., CH_2CH=C), 8.70 (1H, b.s., CO_2H). The mass spectrum showed the parent ion at M^+ = 274 (Calcd. for $C_{17}H_{22}O_3$; M^+ = 274).

Anal. Calcd. for $C_{17}H_{22}O_3$: C, 74.42; H, 8.08

Found: C. 74.26; H, 7.99.

Esterification of Compound 83: Preparation of Dienone 84

The crude acid 83 (110 g) was dissolved in methanol and esterified with diazomethane in ether. Approximately 20 g of diazomethane was required to complete the esterification. After evaporating the solvent *in vacuo* 112 g of material in the form of a reddish syrup was obtained. Crystallization from ether yielded a few grams of the esterified dienone 84, m.p. 110-111°C, in the form of a white crystalline solid. The infrared spectrum (KBr) gave absorptions at ν_{max} 1710 cm^{-1} (ester), 1650 cm^{-1} (α,β-unsaturated ketone), 1570 cm^{-1} (conjugated double bond). The NMR spectrum ($CDCl_3$) gave signals at δ 0.97 (3H, S, C-CH_3), 1.24 (3H, S, C-CH_3), 3.73 (3H, S, O-CH_3), 5.90 (1H, S, C=CH-C=O), 6.15 (1H, b.s., CH_2-CH=C). The mass spectrum gave the parent ion at M^+ = 288 (Calcd. for $C_{18}H_{24}O_3$; M^+ = 288).

Anal. Calcd. for $C_{18}H_{24}O_3$: C, 74.96; H, 8.39

Found: C, 74.77; H, 8.37.

Sodium Borohydride Reduction of Dienone 84: Preparation of Alcohol 85

The crystalline dienone 84 (100 g) was dissolved in absolute ethanol (700 ml). Sodium borohydride (30 g) was dissolved in water (200 ml) and absolute ethanol (50 ml). The solution containing sodium borohydride was added slowly to dienone 84 and was allowed to react for 20 hours. The solution was evaporated *in vacuo* to yield a yellow syrup which was dissolved in ether (200 ml) and 5 per cent aqueous sodium chloride solution (200 ml). After shaking, the ether layer was removed and the aqueous layer was extracted twice with ether (100 ml). The combined ether extracts were washed twice with 5 per cent aqueous sodium chloride (100 ml), dried over anhydrous magnesium sulfate, and evaporated *in vacuo* to yield 85 as a yellow syrup (99 g). The infrared spectrum (film) showed absorptions at 3350 cm^{-1} (characteristic of a hydroxyl group), 1700 cm^{-1} (ester), 1650 cm^{-1} and 1600 cm^{-1} (conjugated double bonds).

Acetylation of Alcohol 85: Preparation of Ester-acetate 86

Alcohol 85 (97.4 g) was dissolved in dry pyridine (250 ml) and acetic anhydride (250 ml) and allowed to stand at room temperature overnight. After addition of ether (1000 ml), the solution was extracted twice with cool water (1000 ml), cool 5 per cent hydrochloric acid (100 ml) and again with water (1000 ml). The solution was dried over magnesium sulfate and evaporated *in vacuo* to yield 86 as a yellow syrup (106 g). All crystallization attempts failed because of the presence of two epimers. The infrared spectrum showed: ν_{max}^{film} 1710 cm^{-1} (ester and acetate), 1600 cm^{-1} (conjugated double bonds), 1250 cm^{-1}

(characteristic of an acetate). The NMR spectrum ($CDCl_3$) showed signals at δ 0.84 (3H, S, C-CH_3), 1.20 (3H, S, C-CH_3), 2.08 (3H, S, CCH_3), 3.69 (3H, S, C-O-CH_3), 5.5 (2H, multiplet, vinyl).

Epoxidation of Compound 86: Preparation of Epoxide 87

Compound 86 (21.3 g) was dissolved in ether (400 ml), cooled, and stirred in an ice bath. After addition of m-chloroperbenzoic acid (11.26 g) dissolved in dry ether (60 ml), the solution was stirred for one hour at ice bath temperature. The reaction mixture was stirred overnight at room temperature and then treated with 10 per cent aqueous sodium bicarbonate solution (50 ml) to insure that no trace of peracid was left. The solution was washed with four 100 ml portions of 4 per cent aqueous sodium bicarbonate solution until the washings no longer gave a precipitate upon acidification with concentrated hydrochloric acid. The solution was washed thrice with water (100 ml), dried over anhydrous magnesium sulfate, and evaporated *in vacuo* to yield crude 87 (21.9 g) as a yellow syrup. The infrared showed: ν_{max}^{film} 1720 cm^{-1}, 1640 cm^{-1} (weak). The NMR spectrum ($CDCl_3$) gave signals at δ 1.18 (3H, S, C-CH_3), 2.08 (3H, S, O=CCH_3), 3.48 (1H, d, C-CH, J = 7 cps), 3.68 (3H, S, O-CH_3), 5.80 (1H, d, C=CH). There were several peaks in the methyl region δ 0.80-1.10 which were due to the other methyl groups present in the various isomers. Crystallization attempts finally gave a few milligrams of a crude yellow solid, m.p. 158-161°, which could not be purified further. The mass spectrum gave a parent peak at M^+ = 348 (calcd. for $C_{20}H_{28}O_5$; M^+ = 348).

Reaction of Compound 87 with Boron Trifluoride-Etherate: Preparation of Ketone 88

Epoxide 87 (21.9 g) was dissolved in dry benzene (125 ml). After cooling the well-stirred solution to 10°C, boron trifluoride-etherate complex (4 ml) in dry benzene (10 ml), was added. The solution was stirred for 4.5 minutes, decomposed with water (200 ml), and extracted twice with ether (100 ml). The ether extract was washed with water, dried over anhydrous magnesium sulfate, and evaporated *in vacuo* to yield 20.5 g of crude ketone 88 as a yellow syrup. The infrared spectrum showed: ν_{max}^{film} 1710 cm^{-1} (ester), 1650 cm^{-1} (ketone), 1550 cm^{-1}. Crude 88 resisted all crystallization attempts. The complexity of the spectrum of crude ketone 88 indicated the presence of a number of isomers. Since several of these isomers would be eliminated by the next reaction, purification was not attempted at this point.

Isomerization of Ketone 88: Preparation of Dienone 89

Ketone 88 (20.48 g) was dissolved in benzene (20 ml) and adsorbed on an alumina column (350 g, activity II, Merck acid-washed, made up with n-hexane). After allowing the material to remain on the column for two hours, it was eluted with benzene. The GLC analysis (10% SE-30 on 100/120 mesh GCQ column, C.T. 220°C, H.F.R. 88 ml/min) of the second 75 ml fraction showed only one major component with R_t 3.6 min. A total of nine fractions were collected of which the last one showed the absence of any major component on the GLC. Evaporation of fractions two through eight gave dienone 89 (11.5 g) as a yellow viscous liquid. Crystallization from ether yielded a small amount of

pure dienone 89 in the form of a white solid, m.p. 91-92°C of identical R_t and IR which showed: ν_{max}^{KBr} 1725 cm^{-1} (ester), 1650 cm^{-1} (α,β-unsaturated ketone), 1550 cm^{-1} (conjugated double bond). The ultraviolet spectrum showed: λ_{max}^{hexane} 296 mu (ε = 9,100). The NMR ($CDCl_3$) spectrum showed signals at δ 0.99 (3H, S, C-CH_3), 1.27 (3H, S, C-CH_3), 3.72 (3H, S, O-CH_3), 6.3 (2H, b.s., vinyl). The mass spectrum gave the parent ion at M^+ = 288 (Calcd. for $C_{18}H_{24}O_3$; M^+ = 288).

Anal. Calcd. for $C_{18}H_{24}O_3$: C, 74.96; H, 8.39

Found: C, 74.91; H, 8.26.

Reaction of Maleic Anhydride with Dienone 89:
Formation of Adducts 90 and 91

Dienone 89 (1 g) was refluxed for two hours with maleic anhydride (1.4 g) in m-xylene (3.5 ml) containing a trace of trichloroacetic acid. The solvent was evaporated *in vacuo* and the residue was dissolved in ether (50 ml) and then extracted with water (50 ml) five times to remove excess maleic anhydride. The ether layer was dried over anhydrous magnesium sulfate and evaporated *in vacuo* to yield a dark brown syrup (1.5 g). GLC analysis (3% SE-30 on 100/120 mesh GCQ column, C.T. 270°C, H.F.R. 90 ml/min) showed the presence of two adducts (1:1 ratio) in approximately 50 per cent yield with R_t 3.6 and 4.6 minutes. Crystallization from ether yielded 125 mg of a white solid, m.p. 91-92°C, which was shown by GLC analysis using the conditions mentioned above to contain two components (1:1 ratio) with R_t 3.6 and 4.6 minutes. The infrared showed: ν_{max}^{KBr} 1840 cm^{-1} (anhydride), 1770 cm^{-1} (anhydride), 1710 cm^{-1} (ester), and 1600 cm^{-1} (double bond). The NMR (Plate I) spectrum ($CDCl_3$) gave signals at δ 0.85 (3H, S,

C-CH_3), 0.98 (3H, S, C-CH_3), 1.21 (3H, S, C-CH_3), 1.25 (3H, S, C-CH_3), 3.69 (6H, S, 2 O-CH_3), 6.11 (2H, d, J = 7 cps).

Some Diels-Alder Reactions Attempted with Dienone 89

Reaction of Maleic Anhydride with Dienone 89

Procedure I. Dienone 89 (1.0 g) was refluxed with maleic anhydride (1.0 g) in toluene (5 ml) for five hours. GLC analysis (3% SE-30 on 100/120 mesh GCQ column, C.T. 270°C, H.F.R. 90 ml/min) showed two adducts (1:1 ratio) in approximately 50 per cent yield with R_t 1.8 and 2.3 minutes. After esterification with diazomethane, the two adducts were separated by chromatography on an alumina column (80 g, activity II, Merck acid-washed) giving 288 mg of the first adduct and 211 mg of the second adduct.

Procedure II. Dienone 89 (1.0 g) and maleic anhydride (1.4 g) were dissolved in m-xylene (3.5 ml) and allowed to reflux for 1.5 hours with a trace of trichloroacetic acid. The solution was evaporated *in vacuo* and the residue was dissolved in ether (50 ml) and then extracted with water (50 ml) five times to remove excess anhydride. The ether layer was dried over anhydrous magnesium sulfate and evaporated *in vacuo* to yield 1.7 g of crude product. The product was esterified with diazomethane and the two adducts were separated on alumina (80 g column, activity II, Merck acid-washed) as above to yield 280 mg of the first adduct and 266 mg of the second adduct.

Treatment of Dienone 89 with Itaconic Anhydride (92)

Dienone 89 (1.0 g) was dissolved in m-xylene (4 ml) and this was followed by addition of itaconic anhydride (1 g) and a trace of

trichloroacetic acid. After refluxing 6 hours GLC analysis (3% SE-30 on 100/120 mesh GCQ column, C.T. 270°C, H.F.R. 90 ml/min) showed the presence of only starting material. After adding an additional amount of trichloroacetic acid and refluxing for an additional 24 hours, GLC analysis under the same conditions as above showed the presence of only starting material.

Treatment of Dienone 89 with Citraconic Anhydride (93)

Procedure I. Dienone 89 (1.0 g) was dissolved in m-xylene (4 ml) to which was added citraconic anhydride (1.2 g) and a trace of trichloroacetic acid. After refluxing for 24 hours GLC analysis (3% SE-30 on 100/120 mesh GCQ column, C.T. 270°C, H.F.R. 90 ml/min) showed the presence of only starting material.

Procedure II. Dienone 89 (1.0 g) and citraconic anhydride (1.5 ml) were heated in an oil bath at 200°C for seven hours. GLC analysis (3% SE-30 on 100/120 mesh column, C.T. 270°C, H.F.R. 90 ml/min) showed that no adducts were present.

Procedure III. Dienone 89 (0.25 g) was dissolved in benzene (3 ml). After addition of citraconic anhydride (0.40 g), the solution was refluxed overnight. GLC analysis (3% SE-30 on 100/120 mesh GCQ column, C.T. 270°C, H.F.R. 90 ml/min) of the resulting solution failed to show the presence of any new products.

Procedure IV. Citraconic anhydride (1 g) was added to a solution of dienone 89 (0.25 g) in diglyme (5 ml). GLC analysis (3% SE-30 on 100/120 mesh GCQ column, C.T. 270°C, H.F.R. 88 ml/min) showed the formation of no adducts after the solution was allowed to reflux for 24 hours.

Treatment of Dienone 89 with α-Acetoxyacrylonitrile 95

Dienone 89 (500 mg) was dissolved in toluene (3 ml) and α-acetoxyacrylonitrile (1 ml). After allowing the mixture to reflux for 48 hours, GLC analysis (3% SE-30 on 100/120 mesh GCQ column, C.T. 270°C, H.F.R. 90 ml/min) showed the presence of only starting material.

Sodium Borohydride Reduction of Dienone 89: Preparation of Diene-ol 98

Dienone 89 (5 g) was dissolved in absolute ethanol (35 ml) and sodium borohydride (1.5 g) was dissolved in water (10 ml). After allowing the combined solutions to react overnight, the solvent was evaporated *in vacuo*. The resulting residue was equilibrated between ether and 5 per cent aqueous sodium chloride solution. The aqueous layer was then extracted twice with ether. The combined ether extracts were washed with water, dried over anhydrous magnesium sulfate, and evaporated *in vacuo* to yield 4.8 g of alcohol 98 as a yellow syrup. The infrared spectrum showed: ν_{max}^{film} 3600-3100 cm^{-1} (hydroxyl), 1725 cm^{-1} (ester), 1630 cm^{-1} (double bond), 1600 cm^{-1} (double bond).

Diels-Alder Reactions Attempted with Compound 98 and α-Acetoxynitrile

Reaction Attempted Using m-Xylene as the Solvent

Diene 98 (400 mg) was dissolved in m-xylene (2 ml) and α-acetoxyacrylonitrile (1 ml) and allowed to reflux for 24 hours. After the solvent was evaporated *in vacuo*, sodium hydroxide (2 g) dissolved in water (20 ml) was added and the mixture was allowed to reflux for two hours. The solution was poured into water and extracted with ether. The combined ether extracts were washed with water, dried

over anhydrous magnesium sulfate, and evaporated *in vacuo* to yield 330 mg of crude product.

An attempt was made to separate any ketonic material present by refluxing the product with 500 mg of Girard's "T" reagent in methanol for four hours. The solvent was evaporated *in vacuo* and 5 per cent aqueous sodium chloride was added to the mixture. The aqueous solution was extracted with ether. The combined ether extracts were washed with water, dried over anhydrous magnesium sulfate, and evaporated *in vacuo* to give 250 mg of non-ketonic product. The aqueous layer was acidified and then extracted with ether. The ether layer was washed with water, dried over magnesium sulfate, and evaporated *in vacuo* to yield only a trace of a yellow syrup.

Reaction Attempted in Diglyme Solvent

Diene 98 (600 mg) was dissolved in 5 ml of diglyme containing 1 ml of α-acetoxyacrylonitrile and a trace of hydroquinone. The mixture was allowed to reflux for 24 hours under a nitrogen atmosphere. GLC analysis (3% SE-30 on 100/120 mesh GCQ column, C.T. 250°C, H.F.R. 90 ml/min) showed no significant formation of adducts.

Reaction Attempted in Toluene Solvent

Diene 98 (500 mg) was dissolved in toluene (2 ml) containing 2 ml of α-acetoxyacrylonitrile and then was allowed to reflux for 48 hours under a nitrogen atmosphere. GLC analysis (3% SE-30 on 100/120 mesh GCQ column, C.T. 250°C, H.F.R. 90 ml/min) showed no formation of adducts.

Preparation of Intermediate 106

Preparation of Triesters 100 and 101

Dienone 89 (37.4 g) was dissolved in 45 ml of m-xylene (b.p. 139°C). After addition of maleic anhydride (35 g) and a trace of trichloroacetic acid, the mixture was allowed to reflux for two hours. The reaction mixture was taken up in ether and extracted with eight 500 ml portions of water to remove excess maleic anhydride. The ether solution was dried over anhydrous magnesium sulfate and evaporated *in vacuo* to yield 35.4 g of a crude mixture. Methanolic ether solutions of the crude mixture were treated with excess ethereal diazomethane (20 g) to give 36 g of product in the form of a yellow syrup. This mixture was chromatographed over alumina (2214 g, activity II, Merck-acid washed). Elution with benzene gave 9.8 g of 100, m.p. 151-153°C, 7.8 g of 101, m.p. 161-163°C, and 5.3 g of a mixture of the two adducts. The spectral properties of adduct 100 were (Plate III) ν_{max}^{KBr} 1740, 1735, 1720, 1690, 1620 cm^{-1}. ORD (Plate IV) of 100 (0.350 g/100 ml, MeOH), 30.5°: $[\Phi]_{589}$ insignificant; $[\Phi]_{304}$ - 3218.4°; $[\Phi]_{292}$ 0°; $[\Phi]_{264}$ + 10,216°; $[\Phi]_{240}$ + 11,327°; a = -134.34. The NMR ($CDCl_3$) spectrum (Plate II) showed signals at δ 0.98 (3H, S, C-CH_3), 1.24 (3H, S, C-CH_3), 3.46 (3H, S, O-CH_3), 3.51 (3H, S, O-CH_3), 3.60 (3H, S, O-CH_3) and 5.89 (1H, d, C=CH-CH, J = 7 cps). The mass spectrum gave a parent peak at M^+ = 432(calcd. for $C_{24}H_{32}O_7$; M^+ = 432). The spectral properties of adduct 101 were (Plate VI) ν_{max}^{KBr} 1745 cm^{-1}, 1730 cm^{-1}, 1710 cm^{-1}, 1700 cm^{-1}, 1620 cm^{-1}. The NMR ($CDCl_3$) spectrum (Plate V) showed signals at δ 1.10 (3H, S, C-CH_3), 1.19 (3H, S, C-CH_3), 3.43 (3H, S, O-CH_3), 3.48 (3H, S, O-CH_3), 3.61 (3H, S, O-CH_3), 5.80 (1H,

d, vinyl, J = 7 cps). ORD (Plate VII) of 101 (0.350 g/100 ml; MeOH), 28.6°C: $[\Phi]_{589}$ + 197°; $[\Phi]_{299}$ + 592°, $[\Phi]_{289}$ ± 0°; $[\Phi]_{242}$ - 4210°; $[\Phi]_{300}$ - 4940; a = +48.02. The mass spectrum gave a parent ion at M^+ = 432 (calcd. for $C_{24}H_{32}O_7$; M^+ = 432).

Anal. Calcd. for $C_{24}H_{32}O_7$: C, 66.72; H, 7.47

Found for adduct 100: C, 66.84; H, 7.65

Found for adduct 101: C, 66.59; H, 7.51.

Saponification of Triester 100: Preparation of Diacid 103

Triester 100 (9.8 g) in methanol (5 ml) was refluxed for 50 minutes with sodium hydroxide (2.1 g) and water (70 ml). After cooling, the reaction solution was diluted with water (250 ml), acidified with 6N hydrochloric acid, and extracted with ether. The ether layer was washed with water, dried over anhydrous magnesium sulfate, and evaporated *in vacuo* to give diacid 103 (9.4 g) as a white glassy material which resisted crystallization. The spectral properties of 103 were: ν_{max}^{film} 3500-2400 cm^{-1}, 1725 cm^{-1}, 1710 cm^{-1}, 1610 cm^{-1}. The NMR (d-acetic acid) spectrum showed signals at δ 0.99 (3H, S, C-CH_3), 1.20 (3H, S, C-CH_3), 3.69 (3H, S, O-CH_3), 6.25 (1H, d, vinyl, J = 7 cps), 11.3 (2H, S, CO_2H). ORD of 103 (0.384 g/100 ml, MeOH), 33.5°: $[\Phi]_{589}$ insignificant; $[\Phi]_{304}$ - 3,365°; $[\Phi]_{289}$ 0°; $[\Phi]_{258}$ + 6815°; $[\Phi]_{234}$ + 8,415°; a = -101.8. The mass spectrum gave the parent ion at M^+ = 404 (calcd. for $C_{22}H_{28}O_7$; M^+ = 404).

Anal. Calcd. for $C_{22}H_{28}O_7$: C, 65.40; H, 6.99

Found: C, 65.58; H, 7.07.

Hydrogenation of Diacid 103: Preparation of Diacid 105

Diacid 103 (9.0 g) was dissolved in 125 ml of acetic acid. This solution was added to 2.3 g of 5 per cent Pt/C in 50 ml acetic acid. Hydrogen had previously been adsorbed on the surface of the catalyst. Four days later the solution was removed from the hydrogenation apparatus after it had taken up 420 ml of hydrogen (calculated amount 465 ml) at atmospheric pressure. The catalyst was removed by filtration and the acetic acid was evaporated *in vacuo* to yield 9.0 g of a clear viscous material. NMR evidence indicated that only 50 per cent of diacid 103 had been hydrogenated. The procedure outlined above was repeated and after three days the solution was worked up to give 8.6 g of diacid 105 as a white glassy material. Crystallization from methanol yielded a small amount of pure 105, m.p. 289-290°C, of identical R_t and IR in the form of a white solid. ν_{max}^{film} 3500-2400 cm^{-1}, 1725 cm^{-1}, 1705 cm^{-1}; NMR ($CDCl_3$): δ 0.84 (3H, S, C-CH_3), 1.22 (3H, S, C-CH_3), 3.68 (3H, S, O-CH_3), 10.03 (2H, S, CO_2H). ORD of 105 (0.448 g/100 ml, MeOH), 32.5°C: $[\Phi]_{589}$ insignificant; $[\Phi]_{305}$ - 977.6°; $[\Phi]_{294}$ 0°; $[\Phi]_{260}$ + 4283.3°; $[\Phi]_{235}$ + 5432.3°; a = -52.60. The mass spectrum gave a parent peak at M^+ = 406 (calcd. for $C_{22}H_{30}O_7$; M^+ = 406).

Anal. Calcd. for $C_{22}H_{30}O_7$: C, 65.08; H, 7.45

Found: C, 65.00; H, 7.58.

Decarboxylation of Compound 105: Preparation of 106

Diacid 105 (6.5 g) was dissolved in dry pyridine (140 ml) and maintained at 70°C under a nitrogen atmosphere. Lead tetraacetate (7 g) was added to the vigorously stirred solution and after ten

minutes an additional 3.5 g was added. After allowing the solution to reflux for 1.5 hours, the pyridine was evaporated *in vacuo* and the residue was acidified with 6N hydrochloric acid (150 ml). The aqueous layer was extracted several times with ether. The combined ether extracts were dried over anhydrous magnesium sulfate and evaporated *in vacuo* to yield 4.8 g of a yellow syrup. This material was dissolved in benzene and adsorbed on neutral alumina (140 g column, activity II). Elution with benzene gave 1.7 g of crude 106 in the form of a yellow syrup. Crystallization from ethanol gave pure 106, m.p. 108.5-109°C, in the form of a white solid. The infrared spectrum (Plate IX) showed: ν_{max}^{KBr} 1725 cm^{-1} ($O=C-OCH_3$), 1695 cm^{-1} (C=O), 1600 cm^{-1} (C=C). The NMR ($CDCl_3$) spectrum (Plate VIII) showed signals at δ 1.00 (3H, S, C-CH_3), 1.18 (3H, S, C-CH_3), 3.68 (3H, S, O-CH_3), 6.17 (1, d of d, CH=CH-CH, J = 7 cps), 7.00 (1H, d, CH=CH, J = 7 cps). The mass spectrum of 106 gave a parent peak at M^+ = 316 (calcd. for $C_{20}H_{28}O_3$; M^+ = 316). ORD (Plate X) of 106 (0.089 g/100 ml, MeOH), 35.5°C: $[\Phi]_{589}$ insignificant; $[\Phi]_{308}$ - 1279.8°; $[\Phi]_{298}$ 0°; $[\Phi]_{258}$ + 8238.12°; $[\Phi]_{222}$ + 14,220; a = -95.1. CD of 106 (0.002817 moles/l, MeOH), 34°C: [θ] = -47.2.

Anal. Calcd. for $C_{22}H_{30}O_7$: C, 65.08; H, 7.45

Found: C, 65.00; H, 7.58.

Correlation of Compound 100 with Known Compound 68[40,63]

Preparation of Diacid 107

Anhydride 68[40,63] (262 mg) was dissolved in methanol (20 ml). After addition of 10 per cent aqueous sodium carbonate (4 ml), the solution was refluxed for four hours and then acidified with concentrated

hydrochloric acid. The mixture was poured into water (100 ml) and extracted with ether. The combined ether extracts were washed with water, dried over anhydrous magnesium sulfate, and evaporated *in vacuo* to yield compound 107 (244 mg) as a syrup. ν_{max}^{film} 3600-3100 cm^{-1} (OH), 1725 cm^{-1} (C=O), 1700 cm^{-1} (CO_2H), 1600 cm^{-1} (vinyl); NMR ($CDCl_3$): δ 1.00 (3H, S, C-CH_3), 1.10 (3H, S, C-CH_3), 5.38 (1H, b.s., OH, disappeared upon addition of D_2O), 5.93 (1H, d, C=C<u>H</u>-CH, J = cps).

Esterification and Oxidation of Compound 107:
Preparation of Diester-acid 108

After esterifying compound 107 in methanol and ether by addition of diazomethane, diester 108 (250 mg) was dissolved in dry pyridine (5 ml). Chromic anhydride (0.3 g) in pyridine (5 ml) was added and the solution was allowed to stir at room temperature for 18 hours. The resulting brown precipitate was removed by filtration and washed with pyridine. After addition of water (50 ml), the filtrate was extracted with ether. The combined ether extracts were washed with cold 5 per cent hydrochloric acid, and water, and dried over anhydrous magnesium sulfate to yield 200 mg of glassy material. An ether solution of the product was extracted with 10 per cent sodium hydroxide solution. The basic extracts were acidified with concentrated hydrochloric acid and then extracted with ether (300 ml). The ether extract was washed with water, dried over magnesium sulfate, and evaporated *in vacuo* to yield 30 mg of non-crystalline 108. ν_{max}^{film} 3600-2400 cm^{-1} (CO_2H), 1725 cm^{-1} (C=O and O=$COCH_3$), 1700 cm^{-1} (CO_2H), 1600 cm^{-1} (C=C).

Esterification of Compound 108: Preparation of Triester 100

Compound 108 was dissolved in methanol (50 ml) and ether (50 ml) and esterified by addition of excess diazomethane in ether. Evaporation of the solvents yielded 40 mg of crude 100. ν_{max}^{film} 1725 cm^{-1} (ester), 1700 cm^{-1} (C = 0), 1600 cm^{-1} (vinyl); NMR ($CDCl_3$): δ 1.00 (3H, S, C-CH_3), 1.25 (3H, S, C-CH_3), 3.53 (3H, S, O-CH_3), 3.60 (3H, S, O-CH_3), 3.68 (3H, S, O-CH_3), 6.02 (1H, d, J = cps). Mixed injections on the GLC at 270°C with a 3 per cent OV-17 column (6 ft., 1/8 inch diameter, H.F.R. 30 ml/min) showed 100 to be identical with the authentic sample prepared as previously described.

Correlation of Compound 105 with Known Compound 109[40,63]

Saponification and Esterification of Diacid 109: Preparation of Compound 110

Diacid-acetate 109[40,63] (6.6 g) was dissolved in a 7 per cent sodium hydroxide-methanol solution (200 ml). This mixture was allowed to reflux for 1.5 hours. After evaporation of methanol *in vacuo*, the residue was dissolved in water (100 ml). The solution was acidified with concentrated hydrochloric acid and then extracted with ether. The combined ether extracts were washed, dried, and evaporated *in vacuo* to yield 3.0 g of a dark brown syrup. ν_{max}^{film} 3600-3100 cm^{-1}, 1725 cm^{-1}, 1700 cm^{-1}. This material (3.0 g) was dissolved in methanol-ether solution and esterified with excess diazomethane to give diester 110. ν_{max}^{film} 3600-3100 cm^{-1}, 1725 cm^{-1}.

Oxidation and Esterification of 110: Preparation of 111

Kiliani's reagent was prepared by dissolving 60 g of $Na_2Cr_2O_7 \cdot 2H_2O$ in 135 ml of water, 80 g of concentrated sulfuric acid,

and 135 ml of acetic acid. Kiliani's reagent (17 g) was added dropwise to a solution of alcohol 110 (2.34 g) in acetic acid (200 ml) at room temperature and allowed to stand at room temperature for 24 hours. The reaction mixture was poured into water and extracted with ether. The ether extract was washed with water and 5 per cent aqueous sodium bicarbonate solution. Subsequently, it was extracted with 2 per cent aqueous sodium hydroxide solution. The basic solution was acidified and extracted with ether. The combined ether extracts were washed with water, dried over anhydrous magnesium sulfate, and evaporated *in vacuo* to yield 0.7 g of a yellow syrup. ν_{max}^{film} 3600-2400 cm^{-1}, 1725 cm^{-1}, 1700 cm^{-1}.

This material was dissolved in a mixture of methanol and ether and esterified with excess diazomethane in ether. The solvent was evaporated *in vacuo* to yield 111 (0.8 g) as a yellow syrup. ν_{max}^{film} 1725 cm^{-1}. Crystallization from ether yielded a few milligrams of 111, m.p. 142-144°C, as a white solid. ν_{max}^{KBr} 1735 cm^{-1}, 1725 cm^{-1}, 1715 cm^{-1}, 1685 cm^{-1}; NMR ($CDCl_3$): δ 0.92 (3H, S, C-CH_3), 1.20 (3H, S, C-CH_3), 3.63 (3H, S, O-CH_3), 3.67 (3H, S, O-CH_3), 3.74 (3H, S, O-CH_3). ORD of 111 (0.400 g/100 ml, MeOH), 34°C: $[\Phi]_{589}$ insignificant; $[\Phi]_{305}$ - 2,256.8°; $[\Phi]_{294}$ 0°; $[\Phi]_{265}$ + 6,683.6; $[\Phi]_{230}$ + 5815.60; a = -89.4. The mass spectrum showed a parent ion at M^+ = 434 (calcd. for $C_{24}H_{34}O_7$; M^+ = 434).

Anal. Calcd. for $C_{24}H_{34}O_7$: C, 66.41; H, 7.90

Found: C, 66.29; H, 7.75.

Comparison (IR, NMR, MS, GLC) showed it to be identical with the triester obtained by esterification of diacid 105 with excess

diazomethane in ether.

Preparation of Acetate 113

Sodium Borohydride Reduction of Intermediate 106: Preparation of Alcohol 112

Sodium borohydride (0.8 g) was dissolved in water (9 ml) and added to an ethanol solution (25 ml) of intermediate 106 (1.7 g). This mixture was allowed to stand at room temperature for 17 hours. The solvents were evaporated *in vacuo* and the gummy residue was dissolved in water and extracted with ether. The combined extracts were washed with water, dried over anhydrous magnesium sulfate, and evaporated *in vacuo* to yield 1.7 g of 112 as a yellow syrup. ν_{max}^{film} 3600-3000 cm^{-1}, 1725 cm^{-1}, 1610 cm^{-1}.

Acetylation of Alcohol 112: Preparation of Acetate 113

Ester-ol 112 (1.6 g) was dissolved in pyridine (5 ml) and acetic anhydride (4 ml). After standing overnight, the solution was poured into ether and extracted with cold water, 5 per cent hydrochloric acid, and then water again. The ether solution was dried over anhydrous magnesium sulfate and evaporated *in vacuo* to yield 1.7 g of 113 as a yellow syrup which resisted crystallization. The infrared spectrum showed: ν_{max}^{film} 1725 cm^{-1}, 1610 cm^{-1}, 1240 cm^{-1}. The NMR ($CDCl_3$) spectrum gave signals at δ 0.84 (3H, S, C-CH_3) 1.20 (3H, S, C-CH_3), 2.08 (3H, S, O=C-CH_3), 3.65 (3H, S, O-CH_3), 6.13 (2H, d, J = 3 cps). GLC analysis (3% OV-17 on 100/120 mesh GCQ column, C.T. 270°C, H.F.R. 90 ml/min showed mainly one component with R_t 1.0 min (~80%). The GLC-MS of 113 gave the parent peak at M^+ = 360 (calcd. for $C_{22}H_{32}O_4$; M^+ = 360).

Attempted Functionalization of the C/D Ring of Compound 113

Attempts to Hydroborate Compound 113

Procedure I (Internal Formation of Diborane). A mixture of diglyme (10 ml), 2-methyl-2-butene (0.6 g), and sodium borohydride (150 mg) was cooled (ice bath), flushed with nitrogen, and stirred while 1 ml of boron trifluoride-etherate was added dropwise. After this solution had been allowed to stand for an additional hour at 0°C, a tetrahydrofuran solution (10 ml) of compound 113 (250 mg) was added. The reaction was permitted to warm up to room temperature (6 hours) and then oxidized by dropwise addition of a solution of 1N sodium hydroxide (5 ml) and 30 per cent hydrogen peroxide (5 ml) at 0°C. The reaction mixture was extracted with ether. The ether extract was washed four times with water to remove diglyme, dried over anhydrous magnesium sulfate, and evaporated *in vacuo* to yield 250 mg of a non-crystalline product.

A solution of 250 mg of the hydroborated product in 5 ml of dry pyridine was added to 0.4 g of chromic anhydride in 6 ml of pyridine which had been cooled to ice bath temperatures. The reaction mixture was stirred for eight hours and then poured into ice water. The aqueous solution was extracted with ether. The combined ether extracts were washed with 5 per cent hydrochloric acid, washed with water, dried over anhydrous magnesium sulfate, and evaporated *in vacuo* to yield 250 mg of non-crystalline product. ν_{max}^{film} 1730, 1650, 1600 cm^{-1}. GLC analysis (3% OV-17 on 100/120 mesh GCQ column, C.T. 260°C, H.F.R. 90 ml/min) showed the presence of eight components with R_t 1.4, 2.0, 2.2, 2.4, 3.0, 3.6, 5.2, and 5.8 min (15:4:12:9:11:22:5:22). Because of

the complex mixture of products formed, no further work was attempted using these reaction conditions.

Procedure II (External Formation of Diborane). Compound 113 (100 mg) was dissolved in 100 ml of THF and poured into a 250 ml flask fitted with a gas bubbling tube. Sodium borohydride (1 g) was dissolved in 100 ml of diglyme and placed in a dropping funnel. Dry ether (10 ml) and boron trifluoride-etherate (10 ml) were placed in a three-necked round-bottomed flask. After the system was flushed with nitrogen for 15 minutes, the sodium borohydride solution was added dropwise and the resulting diborane was carried with nitrogen into the THF solution. The solution was oxidized by adding a few drops of a mixture of 4 per cent sodium hydroxide and 30 per cent hydrogen peroxide to yield 100 mg of a non-crystalline product.

A solution of 100 mg of the hydroborated product in 5 ml of dry pyridine was added to 0.2 g of chromic anhydride in 4 ml of dry pyridine. The reaction mixture was allowed to stir overnight at room temperature and then poured into ice water. The aqueous solution was extracted with ether. The combined ether extracts were washed with 5 per cent hydrochloric acid and water, dried over anhydrous magnesium sulfate and evaporated *in vacuo* to yield 100 mg of non-crystalline product. ν_{max}^{film} 1730 cm^{-1}. GLC analysis (3% OV-17 on 100/120 mesh GCQ column, C.T. 260°C, H.F.R. 90 ml/min) showed the presence of nine components with R_t 1.4, 1.5, 1.8, 2.6, 3.8, 4.3, 5.2, 7.1, 8.0 min (5:3:19:15:8:16:8:13:15). Because of the complexity of this mixture no further work was attempted using hydroboration techniques.

Epoxidation of Compound 113: Formation of Epoxide 114

m-Chloroperbenzoic acid (110 mg) dissolved in ether (4 ml) was added to a solution of compound 113 (110 mg) in dry ether (4 ml). The mixture was allowed to stir for one hour at 0°C and at room temperature for 20 hours. The reaction mixture was poured into ether (300 ml). The organic layer was washed with 5 per cent aqueous sodium bicarbonate and water, dried over anhydrous magnesium sulfate, and evaporated *in vacuo* to yield epoxide 114 as a yellow syrup which resisted all crystallization attempts. GLC analysis (3% SE-30 on 100/120 mesh GCQ column, C.T. 210°C, H.F.R. 90 ml/min) showed two components with R_t 7.4 and 8.0 min (60:40) which were due to the *endo* and *exo* epoxides. The infrared spectrum showed: ν_{max}^{film} 1725 cm^{-1} (broad). The NMR ($CDCl_3$) spectrum gave signals at δ 0.82 (3H, S, C-CH_3), 1.17 (3H, S, C-CH_3), 2.08 (3H, S, O=C-CH_3), 3.63 (3H, S, O-CH_3). GLC-MS analysis (3% SE-30 on 100/120 mesh GCQ column, C.T. 240°C H.F.R. 90 ml/min) gave a parent ion at M^+ = 376 (calcd. for $C_{22}H_{32}O_5$; M^+ = 376).

Attempted Rearrangement of Epoxide 114

A solution of epoxide 114 (78 mg) and boron trifluoride-etherate (0.05 ml) in dry benzene (1.5 ml) and dry ether were kept at 20°C for three hours. The solvent was evaporated *in vacuo* to give a residue which was dissolved in ether. The ether solution was washed with water, dried over anhydrous magnesium sulfate, and evaporated *in vacuo* to yield 78 mg of a non-crystalline product as a yellow syrup. ν_{max}^{film} 1720 cm^{-1}, 1590 cm^{-1}. The rearrangement products were dissolved in methanol (25 ml) along with 200 mg of Girard's "T" reagent. After allowing the mixture to reflux for four hours, the solvent was stripped

off *in vacuo*. The residue was dissolved in 5 per cent aqueous sodium bicarbonate, and extracted with ether. The ether layer was washed with water and dried over anhydrous magnesium sulfate to yield 58 mg of non-ketonic product. The sodium bicarbonate solution was acidified with 6N hydrochloric acid until pH 2 was obtained. After extraction with ether, the combined ether extracts were washed with water, dried over anhydrous magnesium sulfate, and evaporated *in vacuo* to yield 20 mg of a syrup. GLC analysis (3% OV-17 on a 100/120 mesh GCQ column, C.T. 240°C, H.F.R. 90 ml/min) showed only one peak with R_t 3.0 min. The NMR ($CDCl_3$) showed only one large peak at 1.25 δ. Therefore it was concluded that this reaction did not give the desired product.

Treatment of Compound 113 with Nitrosyl Chloride

Procedure I (Reaction at -60°C). Ester-acetate 113 (100 mg) was dissolved in chloroform (12 ml) and cooled to -60°C in a dry ice-acetone bath. Nitrosyl chloride was bubbled through the rapidly stirred solution until the initial blue color was replaced by a yellow-brown color indicative of excess nitrosyl chloride. Hexane (15 ml) which had been cooled to -60°C was added to the solution which was allowed to stir for an additional 30 minutes. The solution was evaporated *in vacuo* to yield 100 mg of a crude product. In an attempt to convert the product to a mixture of ketones it was dissolved in acetic acid (4 ml) and 2N hydrochloric acid (1 ml) and stirred at 75°C for 45 minutes. The reaction mixture was diluted with water and the resulting solution was extracted with ether. The combined ether extracts were washed with water and 5 per cent aqueous sodium bicarbonate, dried over anhydrous magnesium sulfate, and evaporated *in vacuo* to yield 95 mg of a crude

product in the form of a yellow syrup. All data (NMR, GLC, IR) showed this to be starting material, compound 113.

Procedure II (Reaction at 0°C). The ester-acetate 113 (95 mg) recovered from the above experiment was dissolved in chloroform (10 ml) and the solution was cooled in an ice bath. Nitrosyl chloride was bubbled through the rapidly stirred solution until the initial blue color was replaced with a yellow-brown color characteristic of excess nitrosyl chloride. The solution was then evaporated *in vacuo* to yield 100 mg of a product as a yellow syrup. An NMR ($CDCl_3$) of the crude product showed no vinyl protons. The crude product was dissolved in acetic acid (15 ml) and 2N hydrochloric acid (1 ml) and stirred at 75°C for 45 minutes. The solution was poured into water and extracted with ether. Then combined ether extracts were washed with water and 5 per cent aqueous sodium bicarbonate solution, dried over anhydrous magnesium sulfate, and evaporated *in vacuo* to yield 100 mg of a crude product in the form of a dark-brown syrup. GLC analysis (3% SE-30 on 100/120 mesh GCQ column, C.T. 250°C, H.F.R. 90 ml/min) showed the crude product to be a complex mixture containing eight major components with R_t 1.0, 1.2, 2.0, 2.4, 3.0, 3.6, 4.2, 5.0 min (26:12:13:20:7:10:9:37). This reaction was not pursued further because high yields of the desired product could not be isolated from this complex mixture.

Diels-Alder Reactions Attempted in Sealed Tubes

Attempted Reaction of Diene 98 with α-Acetoxyacrylonitrile

Procedure I (Reaction at 150°C for 36 Hours). A mixture of diene 98 (1 g), α-acetoxyacrylonitrile (2 ml), and hydroquinone (25 mg)

was heated under a nitrogen atmosphere in a sealed tube at 150°C for 36 hours. The black residue was dissolved in ether and the solid particles were removed by filtration. The ether layer was dried over anhydrous magnesium sulfate and evaporated *in vacuo* to yield 1.4 g of a brown syrup. This material was heated with 3 g of sodium hydroxide in 30 ml of water under a nitrogen atmosphere for two hours. After cooling, the solution was poured into water (100 ml) and extracted with ether. The ether layer was dried over anhydrous magnesium sulfate and evaporated *in vacuo* to yield a yellow syrup (700 mg). GLC analysis (3% SE-30 on 100/120 mesh GCQ column, C.T. 270°C, H.F.R. 90 ml/min) showed no significant formation of adducts.

Procedure II (reaction at 200°C for Three Hours). Diene 98 (1 g) was dissolved in α-acetoxyacrylonitrile (2 ml) and heated in a sealed tube at 190-210°C for three hours. The material was dissolved in ether and the resulting black solid particles were removed by filtration. The ether layer was dried over anhydrous magnesium sulfate and evaporated *in vacuo* to yield 1.1 g of a yellow syrup. This material was chromatographed on alumina (40 g, neutral, activity II). GLC analysis (3% SE-30 on 100/120 mesh GCQ column, C.T. 270°C, H.F.R. 90 ml/min) of all fractions collected failed to show the presence of any new adducts.

Attempted Reaction of Dienone 89 with α-acetoxyacrylonitrile

Dienone 89 (1 g) was dissolved in α-acetoxyacrylonitrile (2 ml) and placed in a sealed tube at 200°C for five hours. The material was dissolved in ether and the resulting black solid was removed by filtration. The ether layer was dried over anhydrous magnesium sulfate and evaporated *in vacuo* to yield 1.1 g of a brown syrup. GLC analysis (3%

SE-30 on 100/120 mesh GCQ column, C.T. 270°C, H.F.R. 90 ml/min) failed to show any significant formation of adducts.

Diels-Alder Reactions of Dienone 89 with Citraconic Anhydride (93)

Citraconic anhydride (2.0 ml) and dienone 89 (500 mg) were placed in a sealed tube at 150°C for 48 hours. GLC analysis (3% SE-30 on 100/120 mesh GCQ column, C.T. 242°C, H.F.R. 90 ml/min) showed the formation of two adducts with R_t 4.8 and 5.6 min (20:10). Chromatography on silica gel (40 g) gave approximately 200 mg of a mixture (2:1) of pure adducts in white crystalline form, m.p. 170-180°C ν_{max}^{film} 1840 cm^{-1}, 1775 cm^{-1}, 1720 cm^{-1}, 1705 cm^{-1}, 1625 cm^{-1}. The NMR ($CDCl_3$) spectrum gave signals at δ 0.84 and 0.96 (3H, 2:1 ratio), 1.20 (3H, S), 1.48 and 1.57 (3H, 2:1 ratio), 3.68 (3H, S, O-CH_3), 4.11 and 4.16 (1H, d, 2:1 ratio, J = 7 cps).

Repeated chromatography gave 300 mg of the first adduct with R_t 4.8 min in 85 per cent purity, m.p. 175-180°C, ν_{max}^{KBr} 1840 cm^{-1}, 1775 cm^{-1}, 1720 cm^{-1}, 1705 cm^{-1}, 1625 cm^{-1}. The NMR ($CDCl_3$) spectrum gave signals at δ 0.84 (3H, S, C-CH_3), 1.20 (3H, S, O-CH_3), 1.48 (3H, S, C-CH_3), 3.68 (3H, S, O-CH_3), 4.11 (1H, d, J = cps). The mass spectrum gave a parent ion at M^+ = 400 (calcd. for $C_{23}H_{28}O_6$; M^+ = 400).

In order to optimize the yield of these adducts, the reaction was carried out using the procedure described above (unless otherwise indicated) at various temperatures and times. The reaction conditions and results are listed below.

Temperature °C	Time	% 1st Adduct	% 2nd Adduct
125	48 Hours	6.43	3.09
125	96 Hours	9.12	4.47
125	10 Hours	19.2	11.1
142	50 Hours	18.5	3.1
142	4 Days	15.3	8.1
142	10 Days	19.0	8.7
150	3.5 Hours	-	-
150	24 Hours	10.6	5.8
150	48 Hours	20.6	10.0
150	64 Hours	18.7	10.5
150	48 Hours*	29.0	18.3
210	24 Hours	6.37	1.1
210	48 Hours	-	

*110 Fold excess of 93.

Attempted Hydrogenation of the Diels-Alder Adducts Obtained from the Reaction of Citraconic Anhydride with Diene 89

A mixture of the adducts (150 mg) in crystalline form was dissolved in acetic acid. After addition of 5 per cent Pt/C (60 mg), this solution was allowed to remain in the presence of excess hydrogen at 30 p.s.i. and room temperature for six days. The catalyst was removed by filtration and the solvent was evaporated *in vacuo* to yield 150 mg of starting material. That the adducts were not hydrogenated was shown by the presence of an absorption at 1625 cm^{-1} in the infrared spectrum and by the presence of an absorption for one proton at δ 4.11 in the vinyl region of the NMR spectrum. The procedure, described above, was repeated using 362 mg of 5 per cent Pt/C for two days with the same result.

Attempted Preparation of Compound 94

Esterification of the Adducts Obtained from the Diels-Alder Reaction Between Dienone 89 and Citraconic Anhydride (93)

A mixture of the two adducts (800 mg) was dissolved in ether and methanol. Excess diazomethane in ether was added until a yellow color persisted. After excess diazomethane had been allowed to evaporate, the solvents were removed by evaporation *in vacuo* to give 800 mg of a mixture of triesters in the form of a crystalline solid. Chromatography on alumina (neutral, activity II, 40 g) gave a fraction in the 50 per cent cyclohexane-50 per cent benzene eluent which showed only one component with R_t 4.7 min according to GLC analysis (3 per cent SE-30 on 100/120 mesh GCQ column, C.T. 250°C, H.F.R. 90 ml/min). Evaporation *in vacuo* of this fraction gave 120 mg of a triester with R_t 4.7 min in crystalline form, m.p. 92-95°C. ν_{max}^{KBr} 1730 cm^{-1} (broad), 1690 cm^{-1}, 1605 cm^{-1}. The NMR ($CDCl_3$) spectrum showed signals at δ 0.84 (3H, S, C-CH_3), 1.18 (3H, S, C-CH_3), 1.65 (3H, S, C-CH_3), 3.57 (3H, S, O-CH_3), 3.59 (3H, S, O-CH_3), 3.68 (3H, S, O-CH_3), 6.25 (1H, d, C=CH-CH, J = 7 cps). The mass spectrum gave a parent ion at M^+ = 446 (calcd. for $C_{25}H_{34}O_7$; M^+ = 446). The second adduct could not be obtained in pure form.

Saponification of the Triester with R_t 4.7 Min

The triester with R_t 4.7 min (120 mg) was dissolved in a solution containing diethylene glycol (10 ml) sodium hydroxide (1g) and water (3 ml). This solution was heated at 95°C for four hours. After the solution was allowed to cool, it was poured into water (50 ml), acidified with concentrated hydrochloric acid, and extracted with ether.

The combined ether extracts were washed with water, dried over magnesium sulfate and evaporated *in vacuo* to yield 120 mg of a yellow syrup. ν_{max}^{film} 3600-2400 cm^{-1}, 1710 cm^{-1}, 1690 cm^{-1}, 1610 cm^{-1}. There were also absorptions at 1840 cm^{-1} and 1775 cm^{-1} present in the infrared spectrum indicating the partial formation of the anhydride adduct with R_t 4.8 min. The complex NMR ($CDCl_3$) spectrum showed the presence of only one methoxy group at δ 3.67 (3H, S) and approximately two acid protons at δ 8.00.

Attempted Hydrogenation of the Crude Diacid Mixture

The crude diacid mixture (120 mg) was dissolved in acetic acid (9 ml). After addition of 5 per cent Pt/C (149 mg), the solution was allowed to remain in the presence of hydrogen at 30 p.s.i. for three days. The catalyst was removed by filtration and the solvent was evaporated *in vacuo* to give 120 mg of crude material. The NMR ($CDCl_3$) spectrum indicated (by integration of the vinyl protons) that approximately 30 per cent of the crude material had been hydrogenated. The crude material (120 mg) was again dissolved in acetic acid (9 ml). After 5 per cent Pt/C (300 mg) had been added, the material was allowed to react with hydrogen at 30 p.s.i. for 6 days. Integration of the NMR ($CDCl_3$) spectrum indicated that no further hydrogenation had occurred.

Decarboxylation of the Mixture Obtained from Hydrogenation of the Crude Diacid Mixture

The crude, partially hydrogenated, material (90 mg) obtained from the previous reaction was dissolved in pyridine (5 ml) and heated to 67°C in an oil bath under a nitrogen atmosphere. Lead tetraacetate

was added and the mixture was allowed to remain at 67°C ± 2 for 45 minutes. The pyridine was evaporated *in vacuo* and the concentrate acidified with 6N hydrochloric acid (50 ml). The aqueous layer was extracted with ether. The combined ether extracts were washed with water, dried over anhydrous magnesium sulfate, and evaporated *in vacuo* to yield 93 mg of a crude product. This crude product was chromatographed on alumina (10 g, neutral, activity II). The first fraction of the benzene eluent contained mainly one component (75%) with R_t 1.4 min (3% OV-17 on 100/120 mesh GCQ column, C.T. 270°C, H.F.R. 90 ml/min). Evaporation of the benzene gave approximately 15 mg of a yellow syrup which resisted crystallization. ν_{max}^{film} 1725 cm^{-1} (strong), 1700 cm^{-1} (medium), 1600 cm^{-1} (weak). A clear NMR spectrum could not be obtained. However, the crude NMR ($CDCl_3$) spectrum showed clear signals at δ 0.68 (3H, S, C-CH_3) and 3.67 (3H, S, O-CH_3). There was also a broad unresolved signal at δ 6.01 which integrated for approximately one proton. There were a number of signals in the region δ 0.80-2.00.

Attempted Formation of Diene 130

Saponification of the Anhydride Adduct with R_t 4.8 Min

The anhydride adduct with R_t 4.8 min (468 mg), which had been obtained in 85 per cent purity by repeated chromatography on silica gel, was dissolved in a solution of methanol (14 ml), water (16 ml), and sodium hydroxide (0.7 g). The solution was refluxed for 45 minutes and poured into water (100 ml). The aqueous layer was acidified and extracted with ether. The combined ether extracts were washed with

water, dried over anhydrous magnesium sulfate, and evaporated *in vacuo* to yield 310 mg of a viscous liquid. ν_{max}^{film} 1840 cm^{-1}, 1780 cm^{-1}, 1720 cm^{-1}, 1620 cm^{-1}.

Attempted Decarboxylation of Crude Mixture Obtained from Saponification of the Anhydride Adduct (R_t 4.8 Min)

The anhydride adduct (300 mg), recovered from the previous reaction, was dissolved in dry pyridine (10 ml). After bubbling oxygen through the solution for 15 minutes, lead tetraacetate (600 mg) was added. The solution was heated in an oil bath at 75°C for 50 minutes. The solution was then poured into dilute nitric acid and extracted with ether. The combined ether extracts were washed with water, dried over anhydrous magnesium sulfate, and evaporated *in vacuo* to yield 280 mg of material. GLC analysis (3 per cent SE-30 on 100/120 mesh GCQ column, C.T. 240°C, H.F.R. 90 ml/min) showed only one new component with R_t 1.8 min (15%). Chromatography on silica gel (10 g) gave, in the chloroform eluent, one compound (60 mg) as a viscous nonvolatile liquid. ν_{max}^{film} 1725 cm^{-1}, 1675 cm^{-1}, 1600 cm^{-1} (strong).

Attempted Hydrogenation of the Anhydride Adduct (R_t 4.8 Min) at High Pressures

Procedure I (Raney Nickel in Basic Solution)

Crude anhydride adduct (138 mg) was dissolved in 6N sodium hydroxide (60 ml). The basic solution was placed inside a metal high-pressure bomb. Raney nickel (w-2, ~ 9 g) was added and the bomb was maintained at 1400 p.s.i. and room temperature for 24 hours. After removing the Raney nickel for filtration, the basic solution was

acidified with concentrated hydrochloric acid and extracted with ether. The combined ether extracts were washed with water, dried over anhydrous magnesium sulfate, and evaporated *in vacuo* to yield 55 mg of crude material in the form of a yellow syrup. The NMR ($CDCl_3$) spectrum showed a one proton doublet at δ 6.10.

Procedure II (platinum in Acetic Acid)

The anhydride adduct (100 mg) was dissolved in 50 ml of acetic containing 300 mg of 5 per cent Pt/C. This solution was placed in a bomb under 1400 p.s.i. and at 100°C for 24 hours. The catalyst was removed by filtration and the solvent was evaporated *in vacuo* to yield 95 mg of a yellow syrup. The NMR ($CDCl_3$) spectrum gave signals at δ 6.10 and 5.35 indicative of vinyl protons.

Decarboxylations Attempted by Electrolysis

Electrolysis of Diacid 103: Preparation of Diene 131

Diacid 103 (1 g) was dissolved in pyridine (40 ml) and triethylamine (1.25 ml). After addition of water (10 ml), the material was electrolyzed at ~ 100 volts (0.5 - 0.8 amps) for about 20 minutes. The mixture was poured into ether. The ether layer was extracted with 5 per cent sodium hydroxide to remove any starting material. The ether layer was washed with water, dried over anhydrous magnesium sulfate, and evaporated *in vacuo* to give 380 mg of a yellow syrup. When crystallization from ether was attempted a white solid, m.p. 172-174°C, was obtained. ν_{max}^{KBr} 1780 cm^{-1}, 1710 cm^{-1}. The NMR ($CDCl_3$) spectrum showed signals at δ 1.15 (3H, S), 1.18 (3H, S), 3.7 (3H, S). An attempt was made to isolate diene 131 using preparative TLC using

silica gel as the sorbent and benzene as the liquid phase. The top fraction was removed and washed with chloroform. The chloroform was evaporated *in vacuo* to yield diene 131 (17 mg), m.p. 86-87°C, in the form of a white solid. ν_{max}^{film} 1720 cm^{-1} (ester), 1690 cm^{-1} (C=O), 1630 cm^{-1} (diene), 1580 cm^{-1} (diene). The NMR ($CDCl_3$) spectrum gave signals at δ 0.93 (3H, S, C-CH_3), 1.21 (3H, S, C-CH_3), 3.69 (3H, S, O-CH_3) and 4.2 (3H, multiplet). The mass spectrum gave a parent ion at M^+ = 314 (calcd. for $C_{20}H_{26}O_3$; M^+ = 314). ORD of 131 (0.400 g/100 ml, MeOH), 26°C: $[\Phi]_{589}$ + 235°; $[\Phi]_{355}$ + 785°; $[\Phi]_{318}$ 0°; $[\Phi]_{306}$ - 471°; $[\Phi]_{298}$ 0°; $[\Phi]_{248}$ + 3,689°; $[\Phi]_{235}$ + 7,536°; a = -41.60.

Anal. Calcd. for $C_{20}H_{26}O_3$: C, 76.43; H, 8.28

Found: C, 76.30; H, 8.11.

Electrolysis of Diacid 105

Diacid (1 g) was dissolved in a mixture of pyridine (90 ml), triethylamine (1.25 ml) and water (10 ml). The mixture was electrolyzed with Platinum electrodes at 100-140 volts and an initial current of 0.8 amps which dropped to 0.1 amps after two hours. The solution was evaporated *in vacuo* and distributed between water and ether. The ether layer was washed with water, 5 per cent aqueous hydrochloric acid, and then water again. The ether solution was dried over anhydrous magnesium sulfate and evaporated *in vacuo* to yield 450 mg of a yellow syrup. GLC analysis (3% SE-30 on 100/120 mesh GCQ column, C.T. 240°C, H.F.R. 90 ml/min) showed it to contain the desired compound 106 (R_t 2 min, 40%) identical with an authentic sample, prepared as previously described, by comparison of its properties (GLC, NMR, IR).

Functionalization of the C/D Ring with Dimethyl Sulfoxide

Acetate-ester 114 (50 mg) was dissolved in 5 ml of dry dimethyl sulfoxide. Air was bubbled through the solution while it was maintained at 100°C for 30 hours. GLC analysis (3% SE-30 on 100/120 mesh GCQ column, C.T. 240°C, H.F.R. 90 ml/min) showed four major components with R_t 2.2, 3.2, 3.6, 3.9 min (49:32:11:8). Mixed injections showed that the compound with R_t 2.2 min was starting material, epoxide 114. GLC-MS analysis (3% SE-30 on 100/120 mesh column, C.T. 250°C) of the compound with R_t 3.2 min gave an ion at m/e 392 (calcd. for $C_{22}H_{32}O_6$; M^+ = 392).

Attempts to Synthesize the Nitrogen-Containing E-Ring of Atidine (2)

Reaction of Hydrazine with Compound 106: Attempted Formation of Hydrazide 119

Hydrazine (1.5 ml) was added to compound 106 (260 mg). After heating the mixture for 15 minutes a small amount of ethanol was added. The mixture was allowed to reflux for 24 hours and then evaporated *in vacuo* to yield 255 mg of a syrup. The GLC analysis and infrared spectrum was identical to that of the starting material, compound 106. The above procedure was repeated and the mixture was allowed to reflux for an additional 24 hours. The reaction mixture was worked up as above to yield 210 mg of a syrup. The lack of a carbonyl band in the infrared spectrum, which could be due to formation of a hydrazide, indicated that the desired compound was not formed. The infrared spectrum showed the disappearance of the peak at 1600 cm^{-1}. This indicated that hydrogenation of the double bond had occurred.

Saponification of Compound 113: Preparation of 120

Compound 113 (550 mg), diethylene glycol (15 ml), potassium hydroxide (2 g), and water (0.5 ml) were heated at 165-170°C for five hours. The solution was acidified with 5N hydrochloric acid and extracted with ether. The combined ether extracts were washed with water, dried over anhydrous magnesium sulfate, and evaporated *in vacuo* to yield 120 (470 mg) as yellow gum. Crystallization from acetone yielded a few milligrams of acid-alcohol 120, m.p. 218-220°C, of identical R_t and IR to the crude material as a white solid. The infrared spectrum showed ν_{max}^{KBr} 3250 cm^{-1} broad, 1690 cm^{-1}. The NMR ($CDCl_3$) spectrum gave signals at δ 0.95 (3H, S, C-CH_3), 1.28 (3H, S, C-CH_3), 6.33 (2H, S, vinyl), 10.53 (1H, S, CO_2H). The mass spectrum gave a parent ion at M^+ = 304 (calcd. for $C_{19}H_{28}O_3$; M^+ = 304).

Anal. Calcd. for $C_{19}H_{28}O_3$: C, 75.06; H, 9.28

Found: C, 74.92; H, 9.29.

Oxidation of Compound 120: Preparation of Keto-acid 121

After dissolving compound 120 (600 mg) in acetone, Jones reagent (4 ml, slight excess) was added dropwise until a bright yellow color persisted. *Iso*-propyl alcohol was added to destroy excess chromium trioxide as evidenced by a blue-green precipitate. A small amount of solid sodium bicarbonate was added to destroy excess sulfuric acid. After the blue-green precipitate was removed by filtration, the solution was evaporated *in vacuo* and the residue was dissolved in ether. The ether solution was washed with water, dried over anhydrous magnesium sulfate, and evaporated *in vacuo* to yield 581 mg of keto-acid

121 in crystalline form. Recrystallization from ether yielded 121, m.p. 182-184°C, in the form of a white solid. The infrared spectrum showed: ν_{max}^{KBr} 3600-2400 cm^{-1} (CO_2H), 1695 cm^{-1} (C=O), 1680 cm^{-1} (CO_2H). The NMR ($CDCl_3$) spectrum showed signals at δ 1.14 (3H, S, C-CH_3), 1.26 (3H, S, C-CH_3), 6.28 (1H, d of d, CH=CH-CH, J = 8 cps), 6.90 (1H, d, C-CH=CH, J = 8 cps), 7.60 (1H, S, CO_2H). ORD of 121 (0.400 g/100 ml, MeOH), 30°C: $[\Phi]_{589}$ + 158.5°; $[\Phi]_{310}$ - 1,506°; $[\Phi]_{299}$ 0°; $[\Phi]_{263}$ + 7134.8°; $[\Phi]_{248}$ + 8,003°; a = -86. The mass spectrum gave a parent ion at M^+ = 302 (Calcd. for $C_{19}H_{26}O_3$; M^+ = 302).

Anal. Calcd. for $C_{19}H_{26}O_3$; C, 75.56; H, 8.68

Found: C, 75.40; H, 8.48.

Treatment of 121 with Thionyl Chloride: Formation of Acid Chloride 122

Compound 121 (184 mg) was dissolved in dry ether (20 ml) to which 5 or 6 drops of pyridine was added. After addition of thionyl chloride (2.5 ml), the solution was allowed to stand at room temperature for three hours. The pyridine hydrochloride was removed by filtration and washed with dry ether. The ether filtrate was evaporated *in vacuo* to yield crystalline acid chloride 122, m.p. 107-110°C. ν_{max}^{film} 1780 cm^{-1} (O=C-Cl), 1700 cm^{-1} (C=O), 1600 cm^{-1} (C=C).

Attempted Formation of Hydrazide 119

Acid chloride 122 (183 mg) was dissolved in a solution of benzene (30 ml) and 95 per cent hydrazine (3 ml) which had been cooled to 0°C. The mixture was vigorously stirred for five minutes and then poured into water (150 ml). The aqueous layer was then extracted with ether. The ether layer was dried over anhydrous magnesium sulfate and

evaporated *in vacuo* to yield 180 mg of a non-crystalline product. ν_{max}^{film} 3500-3100 cm^{-1}, 1650 cm^{-1}. Column chromatography on silica gel (10 g) failed to yield a pure product. The fractions were combined and heated for four hours at 165-170°C in diethylene glycol containing sodium hydroxide (2 g) and water (0.5 ml). The basic solution was extracted with ether. The combined ether extracts were washed with water, dried over anhydrous magnesium sulfate, and evaporated *in vacuo* to yield 134 mg of a non-acidic compound as a yellow syrup. ν_{max}^{film} 3600-3100 cm^{-1}, 1700 cm^{-1} (medium), 1650 cm^{-1} (strong), 1600 cm^{-1} (weak). The aqueous layer was acidified and extracted with ether. The ether layer was dried over anhydrous magnesium sulfate and evaporated *in vacuo* to yield 38 mg of acidic compound as a yellow syrup. ν_{max}^{film} 3600-2400, 1700 cm^{-1}, 1600 cm^{-1}.

Saponification of 106: Preparation of 121

Compound 106 (350 mg), diethylene glycol (13 ml), potassium hydroxide (1.4 g), and water (0.9 ml) were heated at 165-170°C for four hours. The solution was cooled and poured into water (100 ml). After acidification with 6N hydrochloric acid, the aqueous layer was extracted with ether. The ether layer was washed with water, dried over anhydrous magnesium sulfate, and evaporated *in vacuo* to yield 300 mg of keto-acid 121 which had the same properties as described previously.

Attempted Preparation of Lactam 123 via Azide 118

Keto-acid 121 (300 mg) was dissolved in dry ether (20 ml) to which 5 or 6 drops of pyridine was added. After addition of thionyl chloride (2.5 ml), the solution was allowed to stand at room temperature

for three hours. The pyridine hydrochloride was removed by filtration and washed with dry ether. The ether filtrate was evaporated *in vacuo* to yield acid chloride 122 (285 mg) as a syrup. ν_{max}^{film} 1780 cm^{-1}, 1700 cm^{-1}, 1600 cm^{-1}.

The acid chloride 122 (285 mg) in dioxane and sodium azide (1 g) in water (8 ml) were vigorously shaken for five minutes and then extracted with cyclohexane. The organic layer was washed with water, 5 per cent aqueous sodium bicarbonate, water again, and dried over anhydrous magnesium sulfate. This solution, which exhibited infrared adsorptions at 2130 cm^{-1} (azide) and 1715 cm^{-1} (C=0), was irradiated using a Hanovia 450 watt ultraviolet lamp. The cell was cooled with an outside water jacket. The solution in the jacket was maintained at -5°C. While the solution was being photolyzed for four hours the temperature in the cell rose to 40°C. After the photolysis was completed, the solution was evaporated *in vacuo* to give 280 mg of crude material. Chromatography on alumina (13 g, neutral, activity II) gave, in the chloroform eluent, mainly one compound (38 mg) with R_t 3.4 (77%) min according to GLC analysis (3% SE-30 on 100/120 mesh GCQ column, C.T. 252°C, H.F.R. 90 ml/min). The infrared spectrum of the yellow syrup, which resisted all crystallization attempts, showed ν_{max}^{film} 3300 cm^{-1}, 1720 cm^{-1}, 1660 cm^{-1}. A clear NMR spectrum could not be obtained because of the small amount of material and because of a large amount of a long-chained hydrocarbon impurity which gave a signal at 74 cps. GLC-MS analysis (3% SE-30 on 100/120 mesh CW column, C.T. 250°C) of the component with R_t 3.4 min (77%) gave a parent ion at M^+ = 299 (calcd. for $C_{19}H_{25}O_2N$; M^+ = 299).

Preparation of Lactam 123

Keto-acid 121 (581 mg) was dissolved in dry ether (75 ml) to which 15 drops of pyridine was added. After addition of thionyl chloride (7.5 ml), the solution was allowed to stand at room temperature for three hours. The pyridine hydrochloride was removed by filtration and washed with dry ether. The ether filtrate was evaporated *in vacuo* to yield ~ 580 mg of crystalline acid chloride, m.p. 107-110°C. ν_{max}^{film} 1780 cm^{-1}, 1690 cm^{-1}, 1600 cm^{-1}.

Acid chloride 122 (~ 580 mg) was dissolved in dioxane (20 ml) to which sodium azide (1 g) and water (8 ml) added. The solution was shaken vigorously for eight minutes and extracted with cool hexane (0°C). The hexane was dried over anhydrous sodium sulfate and placed in a photolysis cell. The hexane solution of the azide was irradiated using a Hanovia 450 watt ultraviolet lamp in a quartz cell which had a quartz jacket between the lamp and the solution for cooling. The photolysis cell, which had a capacity of 300 ml, also had an external cooling jacket. Cooling was provided by connecting these two jackets to a circulating device which circulated methanol-water solution maintained at 0°C. Evaporation of the hexane solution *in vacuo* gave 700 mg of a yellow syrup. The material was chromatographed on alumina (20 g, activity I, acid-washed). Elution with 60 per cent chloroform-benzene gave approximately 110 mg of pure lactam 123, m.p. 253-255°C, in the form of a white solid. The infrared spectrum (Plate XII) showed: ν_{film}^{KBr} 3200 cm^{-1}, 1700 cm^{-1}, 1650 cm^{-1}, 1620 cm^{-1}. The NMR ($CDCl_3$) spectrum (Plate XI) showed signals at δ 1.17 (3H, S, C-CH_3), 3.68 (2H, d of d, NH-CH_2, J = 13 cps), 6.26 (1H, d of d, J = 8 cps), 6.98

(1H, d, J = 8 cps). ORD (Plate XIV) of 123 (0.730 g/100 ml, MeOH), 31°C: $[\Phi]_{589}$ + 403°; $[\Phi]_{310}$ - 3,160°; $[\Phi]_{292}$ 0°; $[\Phi]_{260}$ + 5,670°; $[\Phi]_{210}$ + 6,900°; a = -88.30. The mass spectrum (Plate XIII) gave a parent ion at M^+ = 299 (calcd. for $C_{19}H_{25}O_2N$; M^+ = 299). The precise mass determination of M_{299} using 1,2-dichloro-octafluoridecyclohexane-1 as the standard gave M^+ = 299.1860 (calcd. M^+ = 299.1885).

CHAPTER V

INTRODUCTION TO THE SYNTHESIS OF ISOTRACHYLOBANE

The diterpenes (or more accurately, the diterpenoids) form a broad group of plant and fungal products containing 20 carbon atoms. Consequently, these compounds are derived from four units of isopentenyl pyrophosphate. The diterpenoids have been studied[64] throughout the long history of terpenoid natural product chemistry. A number of compounds of biological importance have been found among the deterpenes in the last two decades. Indeed, it is now realized that they embrace a wide range of biological activity including antibiotics, plant harmones, cattle poisons, and perfuming constituents.

Dehydrogenation experiments introduced by Vesterburg[65] in 1903 and their subsequent exploitation[66] by Ruzicka form a major advancement in terpenoid chemistry because of the resulting clarification of the carbon skeleta of these polycyclic compounds. Coupled with the application[67] of the Biogenetic Isoprene Rule, clarification of the major constituents of plant resin acids was provided.

It is now recognized that cyclization of geranylgeraniol (134), possibly as its pyrophosphate (see Figure 8) provides a number of classes of diterpenes. The major pathway appears to lead initially to the bicyclic diterpenes, although several schemes may be invoked to account for various polycyclic diterpenes. These may be subdivided *inter alia* into those of the labdane (135) and manool (136) types.

These included a number of resin constituents and a group of interesting bitter principles in which some subsidiary rearrangements have taken

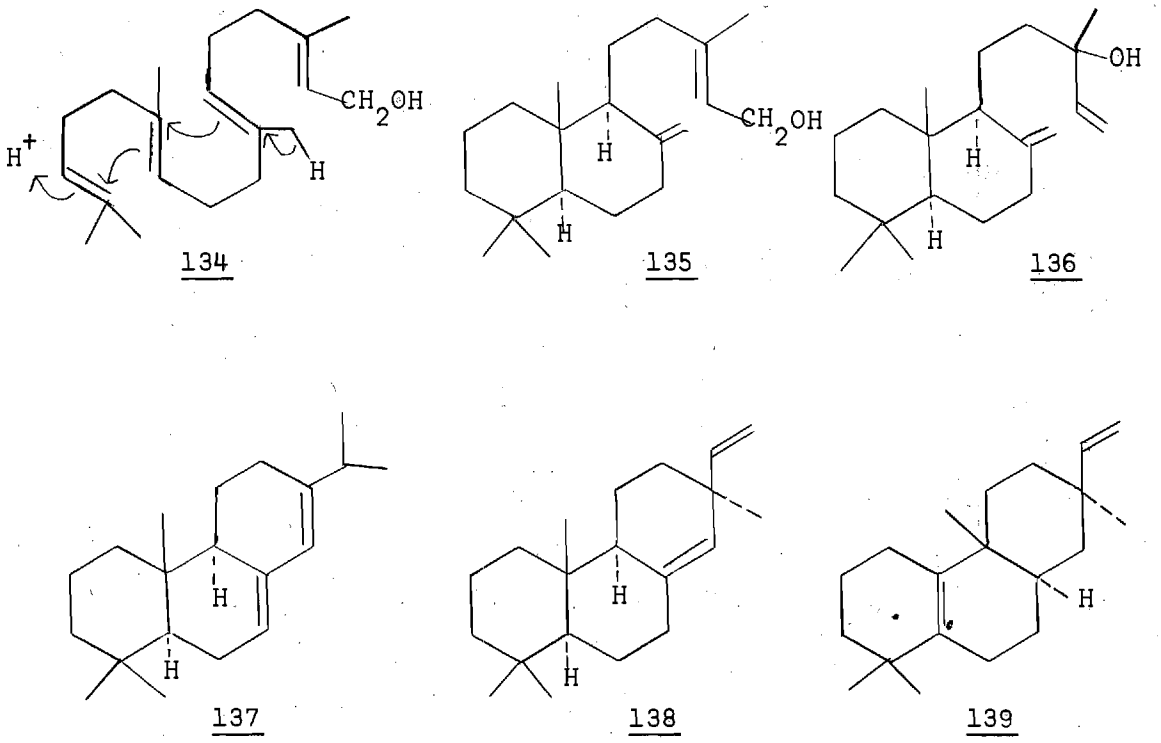


Figure 8. Biosynthesis of the Abietadiene, Pimaradiene, and Rosadiene Skeleta

place. Cyclization of the bicyclic systems leads to the tricyclic abietadiene (137), pimaradiene (138), and rosadiene (139) skeleta, which form the backbone of many of the resin acids and their relatives. Further cyclization of the pimarene series then leads to the tetracyclic diterpenoids.

In 1955 Wenkert[68] suggested that the tetracyclic diterpenes might arise through cyclization of suitably oriented pimaradienes (140) involving a non-classical carbonium ion (see Figure 9). This ion

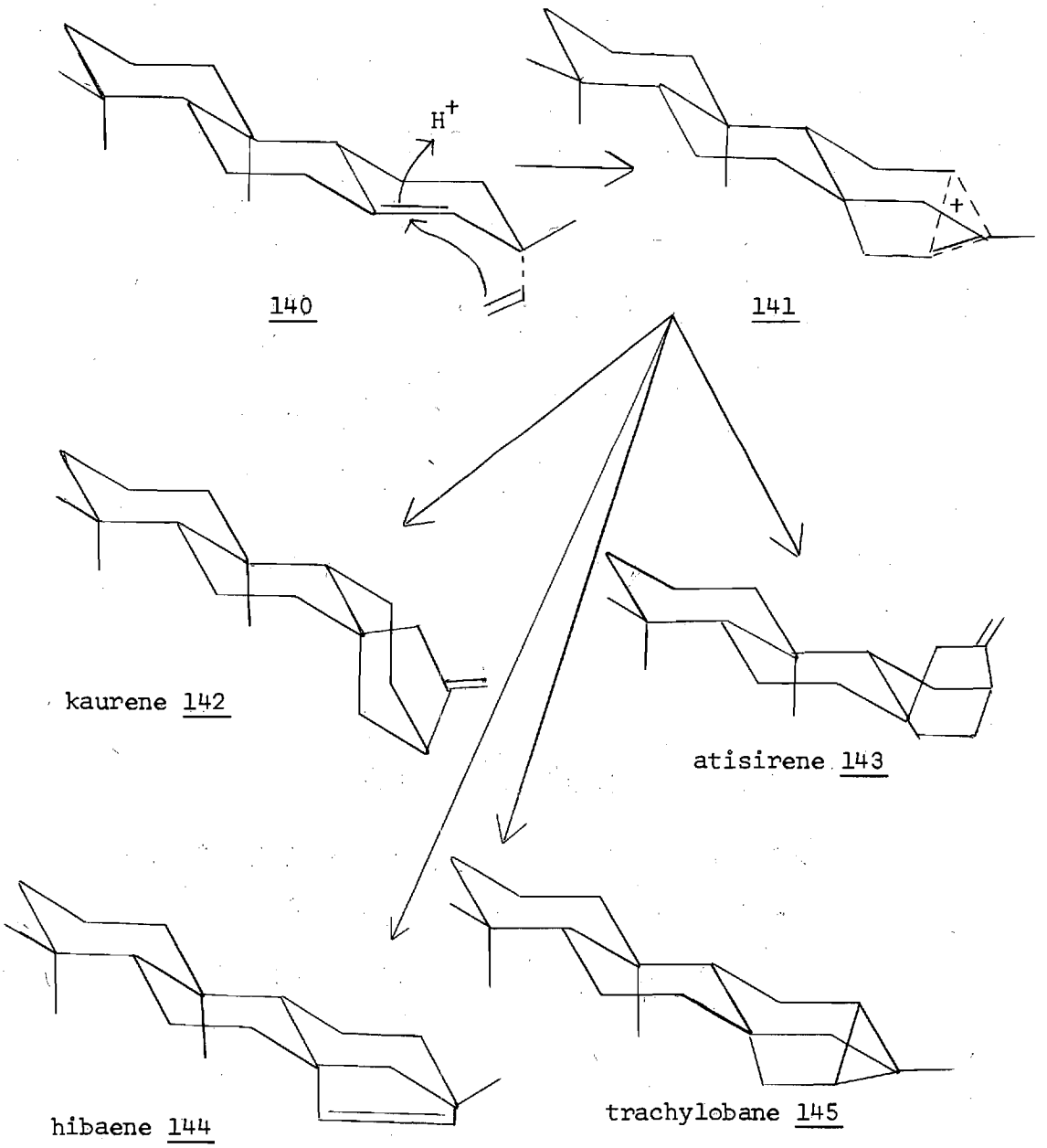


Figure 9. Postulated Biosynthetic Scheme for the Kaurene, Atisirene, Hibaene, and Trachylobane Skeleta

(141) might collapse in a number of ways forming compounds of the kaurene (142), atisine (143) and the hibaene (144) skeleta. Alternatively, cyclization of this ion may lead to the recently discovered[69] pentacyclic trachylobane (145). The co-occurrence[70] of a progenitor of this type (-) - pimaradiene, with its products of cyclization of (-)-hibaene, and atisirine in *Erythoroxylon monogynum* lends valuable support to a theory of this type. Additional evidence is that atisirine[70] (143), hibaene[71] (144), kaurene[72](142), and trachylobane[69] (145) have been isolated from natural sources since the postulation. Furthermore, the *in vitro* synthesis of hibaene from a pimaradiene precursor has been reported.[73]

Investigations into the acid-catalyzed skeletal rearrangement of the diterpene hydrocarbons have been conducted under various conditions in an effort to interrelate the compounds *via* the postulated intermediate. Hibaene (144) was found to rearrange in acidic solutions of benzene, chloroform, or acetonitrile to form the kaurene skeleton (142).[74] Trachylobane (145) formed, in hydrogen chloride-chloroform solutions, the atisirene (143) and kaurene (142) skeletons[75] in a 24:1 ratio while in acetic acid-acetic anhydride-perchloric acid solution, hibaene (144) was obtained in addition to atisirene (143) and kaurene (142).[76] Kaurene has been found to rearrange to the extent of 4 per cent in acidic chloroform. It was concluded that a common intermediate was not attained; however, the role of the solvent system seems to be a very important consideration in the rearrangement.

The formation of neoatisirene (149) isohibaene (150), phyllocladene (148), and isotrachylobane[75,77] (151) (see Figure 10) is predicted

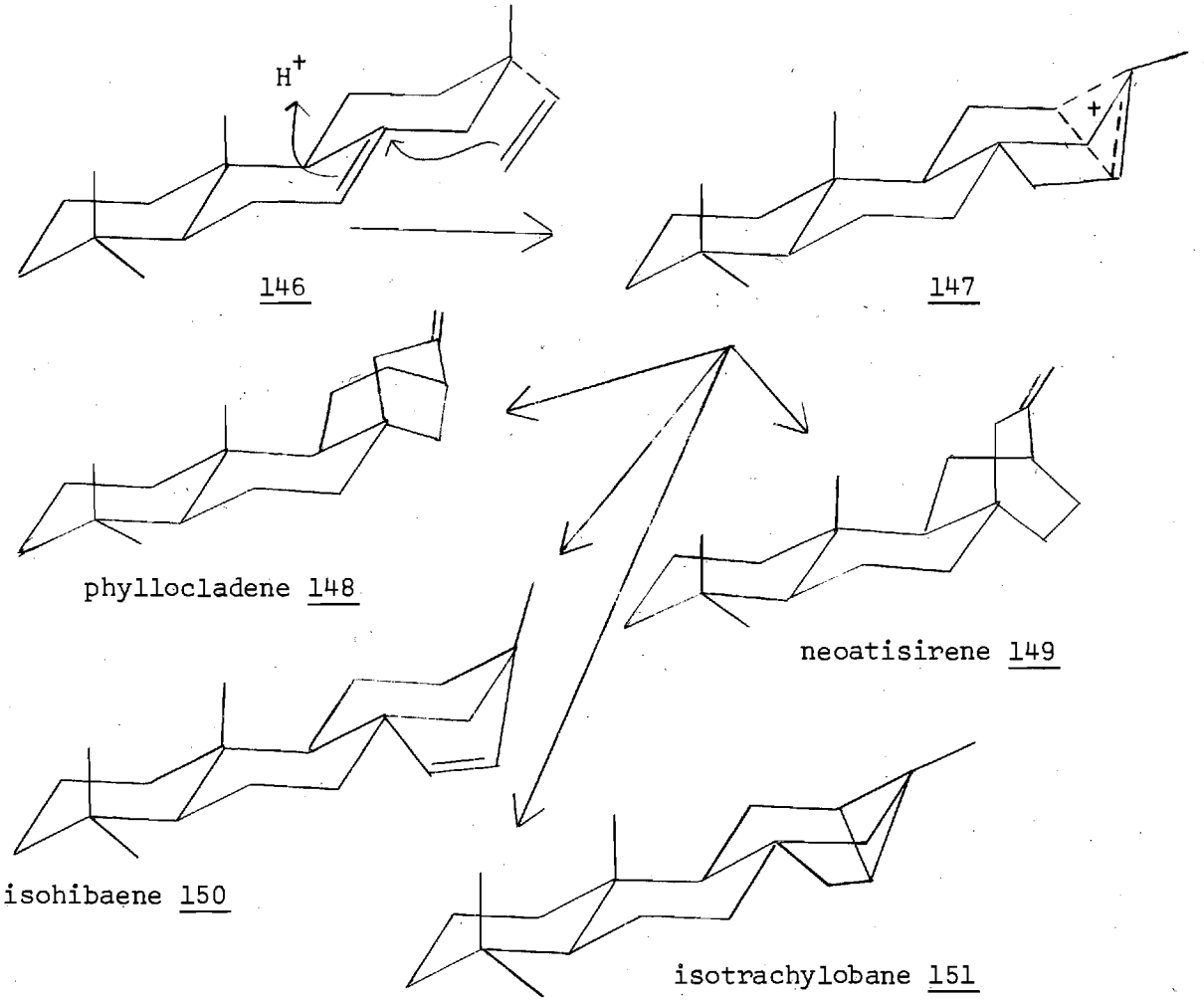


Figure 10. Postulated Biosynthetic Scheme for the Phyllocladene, Isoatisirene, Isohibaene, and Isotrachylobane Skeleta

by extension of Wenkert's postulation to include precursors of the epimeric C-13 pimaradiene (146) type. The phyllocladene (148) skeleton is the only member of this group which has been found in nature. However, the *in vitro* syntheses of isohibaene and isohibane from

isopimaradiene precursors have been reported[78,79] and the synthesis of neoatisirine has been achieved.[77]

The formation of six acetates, three of which have been converted, respectively, into phyllocladene (148), atisirene (143), and neoatisirene (149) has been reported[90] from the acetolysis of the epimeric p-toluenesulfonates of 17-norkauran-16-ol (152). Therefore rearrangement in the absence of the C-17 methyl grouping has interrelated skeletons arising from both postulated biogenetic pathways as shown in Figure 11.

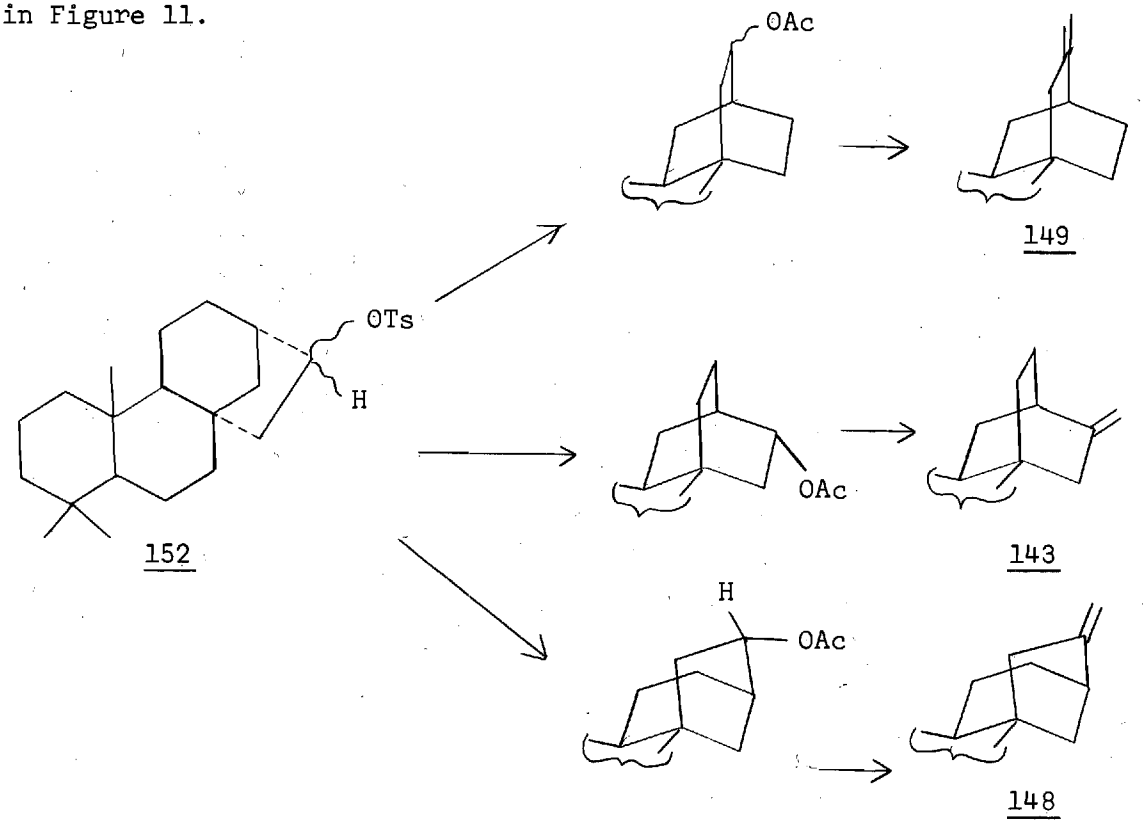
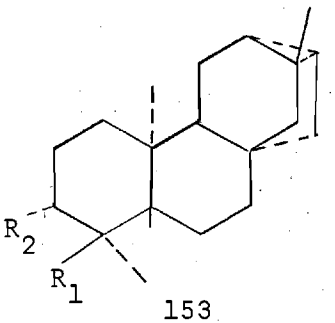


Figure 11. Acetolysis of the Epimeric p-Toluenesulfonates of 17-Norkauran-16-ol

The resin of *Trachylobium verrucosum* known as "Madagascan" or "Zanzibar Copal" contains[69] a number of diterpenes. Among these is a group of compounds possessing the pentacyclic trachylobane skeleton (145). This pentacyclic skeleton represents an interesting stabilized form derived from the non-classical carbonium ion proposed[68] by Wenkert as an intermediate in the biosynthesis of the tetracyclic diterpenes.

Acetylation and reductive removel[69] of the 3-oxygen function led to the correlation of trachylobanic acid (153, $R_1 = CO_2H$, $R_2 = H$) and the corresponding 3-hydroxy (153, $R_1 = CO_2H$, $R_2 = OH$), and the 3-acetoxy (153, $R_1 = CO_2H$, $R_2 = OAc$) acids. Removal of the 3-oxygen function involved the reduction of the 3-tosylhydrazone with lithium aluminum hydride and furnished trachylobanol (153, $R_1 = CH_2OH$, $R_2 = H$) which was also isolated from the resin. Oxidation of the 3-hydroxyl group in 153, $R_1 = CO_2H$, $R_2 = OH$ to a 3-ketone led to prompt decarboxylation indicating a β-hydroxy-acid. A pentacyclic skeleton was indicated by the lack of spectral evidence for a double bond. The nuclear magnetic resonance spectrum of the ester 153, $R_1 = CO_2Me$, $R_2 = H$ contained two high field proton resonances at τ 9.25 and 9.41 indicative of a cyclopropane ring. Dehydrogenation experiments gave rise to four phenanthrene hydrocarbons: pimanthrene, retene, 1-methyl-6-ethyl phenanthrene. A simple fragmentation accounts for each of these products.



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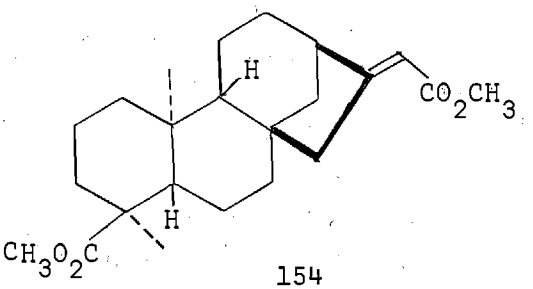

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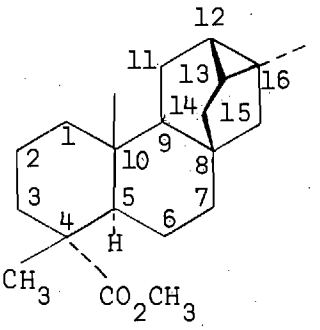
Treatment of the ester 153, $R_1 = CO_2Me$, $R_2 = H$, with perchloric acid in a mixture of acetic acid and acetic anhydride achieved a relationship with the kaurene skeleton. This led to the acylated kaurene derivative 154 which was ozonized to yield a norketone derivative of kaur-16-en-18-oic-acid.

The nuclear magnetic resonance spectra[69] of ester-acetate 153, $R_1 = CO_2Me$, $R_2 = OAc$ indicated an axial hydrogen and an equatorial oxygen function while the spectrum of trachylobanol (153, $R_1 = CH_2$, $R_2 = H$) indicated an equatorial primary alcohol with resonances at τ 6.86. The absolute configuration of the trachylobane series was obtained by application of Horeau's method[80] to the alcohol at position 3 in the corresponding 3-hydroxy-acid (153, $R_1 = CO_2H$, $R_2 = OH$).

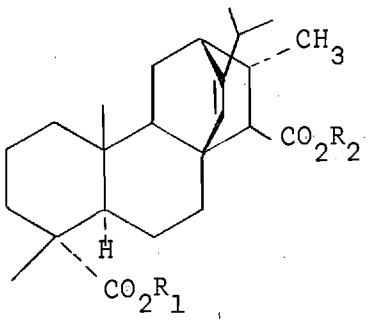
Oxidation of trachylobanol[69] to the aldehyde and subsequent Wolff-Kishner reduction led to the preparation of the parent hydrocarbon, trachylobane (145). The importance of this hydrocarbon is derived from the fact that its discovery completes the set of naturally occurring compounds which may be derived by Wenkert's postulated biogenetic pathway.

Because of their importance, there has been a great interest in the synthesis of compounds possessing the pentacyclic trachylobane skeleton (145). Herz and co-workers[81] have recently reported the synthesis of methyl 13,16-cycloatisan-18-oate (155). the enantiomer of methyl trachylobanate (153; R = Me), which confirmed the structure



methyl 13,-16-cycloatisan-18-oate 155

and stereochemistry assigned previously to the trachylobanes. Their approach involved a Diels-Alder reaction between methyl levopimarate and n-butyl crotonate to yield adduct 156, R_1 = Me, R_2 = Bu in 52 per cent yield. Oxidation of the dibasic acid 156, R_1 = H, R_2 = H with alkaline potassium permanganate in the described[82,83] manner resulted in the formation of lactone 157, R = H. After esterification, lactone 157, R = Me was ozonized to form keto lactone 158 which was converted with chromous chloride to 159. Oxidative decarboxylation of 159 in the presence of cupric acetate as recommended by Kochi[84] gave 160 in 79 per cent yield. Reduction of 160 with tri-t-butoxyaluminum hydride furnished alcohol 161 in 82 per cent yield. When an attempt was made



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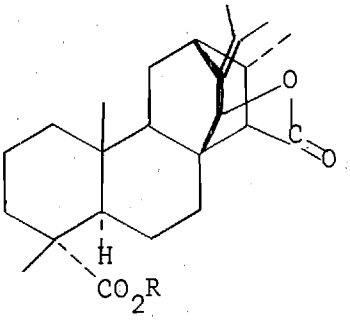

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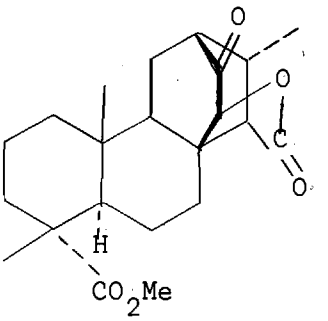
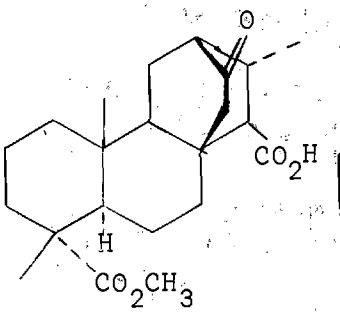


158

to protect the hydroxyl group of 161 through the mesylate prior to hydroboration of the double bond, spontaneous cyclization to compound 162, which possessed the trachylobane skeleton, took place unexpectedly.



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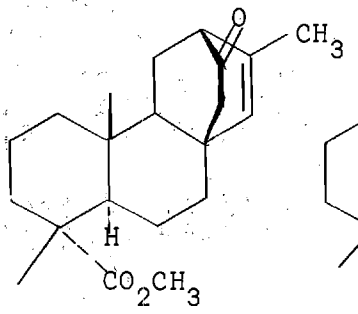

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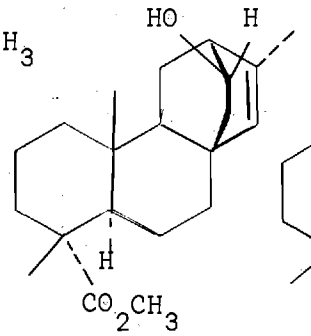

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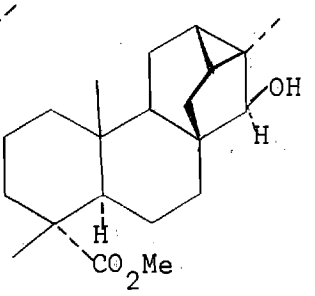
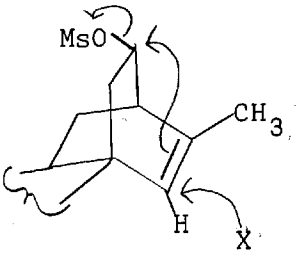


162

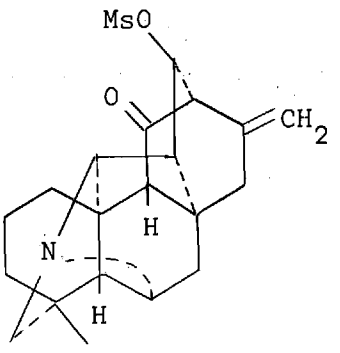
The cyclization of the bicyclo[2.2.2]octenol (161) is formally analogous to the acetolysis of the bicyclo[2.2.2]oct-5-en-2-ol tosylate[85] which leads to the predominant formation of tricyclo-[2.2.2.$0^{2,6}$]octan-3-ol owing to participation by the 2,3 double bond. Hence the formation of 162 might be represented by process B(X = H_2O).



B

When hydride ion was added to a solution of the mesylate it led in 17 per cent yield to methyl anti-trachylobanate (155) which was identical, except rotation, in all respects (IR, NMR, GLC, TLC) to the natural product, methyl trachylobanate. Substitution of boron trifluoride for methanesulfonyl chloride effected a yield improvement to 40 per cent but small amount of contaminants could not be removed.

It is interesting to note that a similar cyclization was obtained by Pelletier[86] and co-workers when the hetisine derivative 163 was treated with lithium aluminum hydride to give 164.



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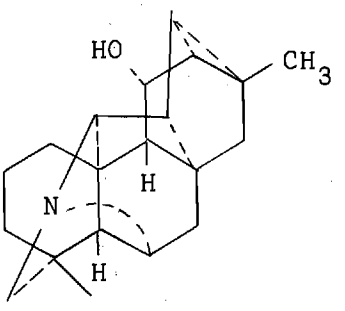


164

The original goal of the work carried out in this laboratory by Gabriel[87] was the synthesis of the enantiomer of trachylobane. The approach involved maleopimoric acid (165) as the starting material. Transformation of 165 into 178 (see Figure 12) involved removal of the isopropyl group of ring C, removal of the anhydride moiety of ring D, and reduction of the acid function of ring A, which had been accomplished previously.[88] The synthesis would have been completed by placement of the methyl group at C-16 and formation of the cyclopropane ring. However, before the synthesis was completed, Herz and co-workers reported the synthesis methyl of anti-trachylobane in a similar route which has already been outlined. Thus, attention was diverted from the original goal.

It was anticipated that the intermediate in the originally proposed synthesis, 178, could lead to isotrachylobane (151), postulated as a possible product arising from an isopimaradiene precursor as mentioned previously.

Treatment of intermediate 178 with methyl magnesium bromide led to the desired tertiary alcohol 179.

In a publication by McCrindle and co-workers,[89] it was shown that tricyclo ($3.2.1.0^{2,7}$) octane (181) can be formed by treating the bicyclic tosylate 180 with lithium aluminum hydride.

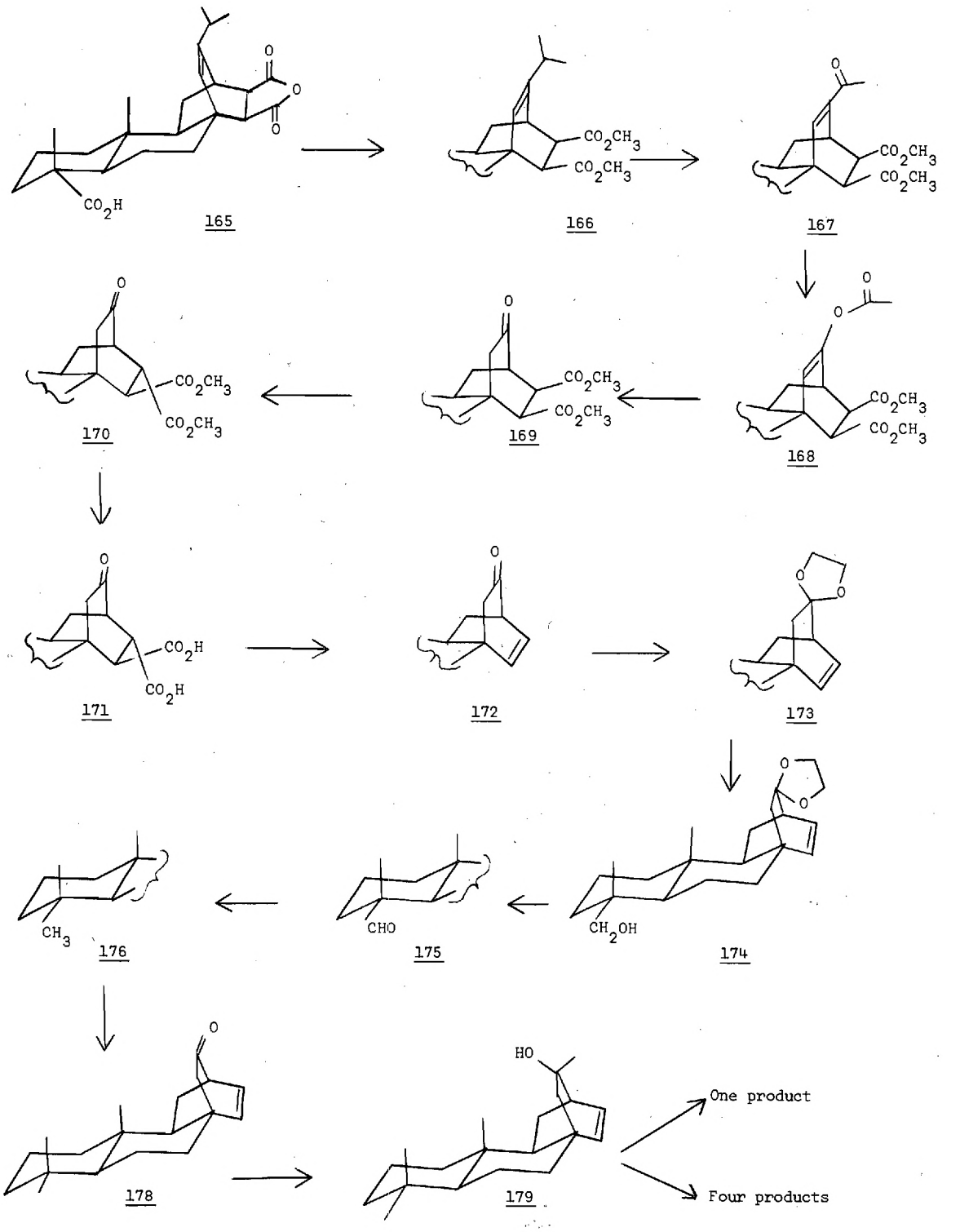
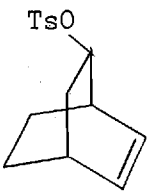
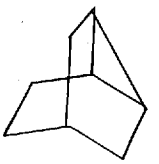


Figure 12. Synthetic Sequence Leading to Intermediate 179



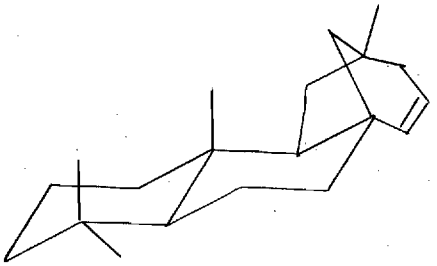
180



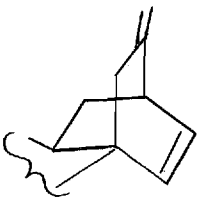
181

An attempt to form the tertiary p-nitrobenzoate of 179, which possessed a similar system, following a procedure by Brown and co-workers[90] failed.

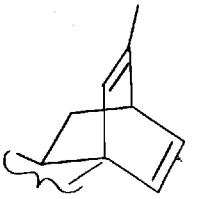
An investigation of the mixed-hydride reduction of 179 was begun. Treatment of 179 with 1:3 lithium aluminum hydride:aluminum chloride led to the formation of a single product which was assigned structure 182.



182



183



184

Treatment of 179 with a 1:1 lithium aluminum hydride:aluminum chloride mixture in di-*n*-butyl ether at reflux temperature resulted in the formation of two products in the ratio of 58:41 as determined by GLC. The major component was assigned structure 183 and the minor product was assigned structure 184. Both of these are consistent since

they could arise from simple dehydration of 179 under the reaction conditions.

The goal of this portion of the thesis was to complete the synthesis of isotrachylobane. It was expected that this would be accomplished by using intermediate 179* under various reaction conditions and with different reagents.

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*The author is indebted to Dr. S. K. Gabriel for the sample which was prepared by procedures given by S. K. Gabriel, Ph.D. Thesis, Georgia Institute of Technology, 1969, Part II.

CHAPTER VI

EXPERIMENTAL PERTAINING TO THE SYNTHESIS OF ISOTRACHYLOBANE

Treatment of Tertiary Alcohol (179) with Lithium Aluminum Hydride

A solution of 179 (82 mg) in dioxane (5 ml), to which lithium aluminum hydride (20 mg) had been added, was allowed to stir overnight at room temperature in a nitrogen atmosphere. GLC analysis (flame) of the crude reaction mixture (3 per cent SE-30 on 100/120 mesh GCQ column, C.T. 180°, H.F.R. 88 ml/min) showed that only starting material was present. The mixture was allowed to reflux overnight under a nitrogen atmosphere, after which, GLC analysis under the same conditions as described above showed that only starting material was present.

Treatment of Tertiary Alcohol (179) with Lithium Aluminum Hydride and Aluminum Chloride (2:1)

A solution of 179 (100 mg) in dioxane (2 ml) was added to dioxane (5 ml) containing a mixture of lithium aluminum hydride (20 mg) and aluminum chloride (35 mg). The solution was allowed to stir overnight at room temperature under a nitrogen atmosphere. GLC analysis (flame) of the crude mixture (3% SE-30 on 100/120 mesh GCQ column, C.T. 180°, H.F.R. 88 ml/min) showed that no change had taken place in the composition of the reaction mixture. After an additional amount of lithium aluminum hydride (40 mg) and aluminum chloride (70 mg) was added, the mixture was allowed to reflux overnight at R.T. under a nitrogen

atmosphere. Excess reagents were destroyed by addition of water. The aqueous layer was extracted with ether, washed with water, dried over anhydrous sulfate, and evaporated *in vacuo* to yield 100 mg of a crude crystalline solid. GLC analysis (flame) of the solid (11% OV-17 + QF-1 on 100/120 mesh GCQ column, C.T. 180°, H.F.R. 88 ml/min) showed this to be starting material, compound 179, with traces of several impurities.

Treatment of Tertiary Alcohol (179) with Lithium Aluminum Hydride and Aluminum Chloride (1:1)

A solution of 179 (100 mg) in dioxane (2 ml) was added to dioxane (5 ml) containing a mixture of lithium aluminum hydride (40 mg) and aluminum chloride (140 mg). The solution was allowed to stir overnight at R.T. under a nitrogen atmosphere. GLC analysis (flame) of the crude reaction mixture (11% QF-1 + OV-17 on 100/120 mesh GCQ column, C.T. 180°, H.F.R. 88 ml/min) showed essentially no change in the composition of the solution. The solution was then allowed to remain at 100°C for three days. After destruction of excess reagents by addition of water, the aqueous layer was extracted with ether. The ether extract was washed with water, dried over anhydrous magnesium sulfate, and evaporated *in vacuo* to yield 90 mg of a nonvolatile liquid. GLC analysis (flame) of the nonvolatile liquid under the same conditions as described above showed it to contain mainly one compound with R_t 6.6 min. The product was shown to be identical to compound 184[87] by NMR and GLC-MS analysis.

Treatment of Tertiary Alcohol (179) with Lithium Aluminum Hydride and Aluminum Chloride (1:3)

A solution of 179 (100 mg) in dioxane (5 ml), which contained lithium aluminum hydride (20 mg) and aluminum chloride (210 mg), was allowed to stir overnight at R.T. under a nitrogen atmosphere. GLC analysis (flame) of the crude reaction mixture (11% QF-1 + OV-17 on 100/120 mesh GCQ column, C.T. 180°, H.F.R. 88 ml/min) showed that essentially no change had occurred in the composition of the reaction mixture.

An additional amount of compound 179 (100 mg) was dissolved in dioxane (5 ml) which was followed by addition of lithium aluminum hydride (30 mg) and aluminum chloride (30 mg). After the mixture had been allowed to stir for ten minutes, GLC analysis (flame) under the same conditions as above showed complete disappearance of starting material. After destruction of excess reagents by addition of water, the aqueous layer was extracted with ether. The ether extract was washed with water, dried over anhydrous magnesium sulfate, and evaporated *in vacuo* to yield 95 mg of a nonvolatile liquid. GLC analysis (flame) of the liquid (11% QF-1 + OV-17 on 100/120 mesh GCQ column, C.T. 180°, H.F.R. 88 ml/min) showed the presence of one major component with R_t, 6.1 min (53%) and three minor components with R_t 2.4, 2.8, and 5.0 min (14:13:19%). Column chromatography of this mixture on 15% silver nitrate-silica gel afforded a nonvolatile liquid (35 mg) in the chloroform eluent. GLC analysis (flame) of the liquid (11% QF-1 + OV-17 on 100/120 mesh GCQ column, C.T. 175°, H.F.R. 88 ml/min) showed one compound with R_t 5.8 min which was identical to that of the retention time given by compound 182.

Treatment of Tertiary Alcohol (179) with Sodium Borohydride and Boron Trifluoride-Etherate at Room Temperature

A solution of 179 (100 mg) in boron trifluoride-etherate (1.26 g), which had been cooled in a dry ice-acetone bath, was added dropwise to a solution of sodium borohydride (11.4 mg) in diglyme (2 ml) at 0°C. The mixture was allowed to stir under nitrogen for 12 hours at room temperature, poured into ice water, and extracted with ether. The ether solution was washed with water, dried over anhydrous magnesium sulfate, and evaporated *in vacuo* to yield 95 mg of a viscous liquid. GLC analysis (flame) of the liquid (3% SE-30 on 100/120 mesh GCQ column, C.T. 180°, H.F.R. 88 ml/min) showed one major product with R_t 2.2 min (68%) which was contaminated with a number of minor components. Separation of the mixture (95 mg) by preparative thin layer chromatography was attempted on silica gel (1 mm) using hexane as a liquid phase. The plate was divided into five fractions which were removed and eluted with chloroform. The top fraction yielded 35 mg of a viscous liquid. GLC analysis (flame) of the liquid (3% SE-30 on 100/120 mesh GCQ column, C.T. 165°C, H.F.R. 88 ml/min) showed one major component with R_t 4.2 min (84%) and one minor component with R_t 0.7 min (14%). Liquid column chromatography of this mixture on silica gel (15% silver nitrate by weight) afforded a single (noncrystalline) compound in the chloroform eluent as shown by GLC analysis under the same conditions as mentioned above. This product appeared to be identical to compound 182[87] by NMR and GLC-MS analysis.

Treatment of Tertiary Alcohol (179) with Boron Trifluoride-Etherate and an Excess of Sodium Borohydride

The tertiary alcohol (179) was dissolved in dioxane (5 ml) followed by addition of sodium borohydride (100 mg) and boron trifluoride-etherate (0.75 g). The mixture was allowed to stir overnight under a nitrogen atmosphere at R.T., poured into ice water, and extracted with ether. The ether solution was washed with water, dried over anhydrous magnesium sulfate and evaporated *in vacuo* to yield 89 mg of a nonvolatile liquid. GLC analysis (flame) of this liquid (11% QF-1 + OV-17 on 100/120 mesh GCQ column, C.T. 180°, H.F.R. 88 ml/min) showed mainly one compound which had the same retention time as compound 184.[87] The NMR was also identical to that shown by compound 184.[87]

Reaction of Tertiary Alcohol (179) with Boron Trifluoride-Etherate and Sodium Borohydride at Low Temperatures: Preparation of Isotrachylobane (151)

A solution of 179 (100 mg) in boron trifluoride-etherate (2.0 g), which had been maintained below 0°C, was added to a solution of sodium borohydride (100 mg) in diglyme (5 ml) at -70°C. The mixture was allowed to remain, with stirring, at -70°C for approximately 45 minutes. After allowing the mixture to stay between -20 and -40°C for two hours, the mixture was allowed to warm up to 0°C, poured into water, and extracted with ether. The ether solution was washed with water, dried over anhydrous magnesium sulfate, and evaporated *in vacuo* to yield a nonvolatile liquid (93 mg). GLC analysis (flame) of the liquid (11% QF-1 + OV-17 on 100/120 mesh GCQ column, C.T. 180°, H.F.R. 88 ml/min)

showed the presence of one major component with R_t 10.4 min (66%) and six minor products with R_t 1.1, 4.8, 5.3, 5.8, 6.1, 6.8 min (6:9:4:7:3:5). Mixed GLC injections showed that the major component corresponded to the starting material, compound 179. The GLC-MS (11% QF-1 + OV-17 100/120 mesh GCQ column, C.T. 180°) showed the parent ions for the last five minor products in the order listed above to be at M^+ = 272, 272, 272, 270, 270 (calcd. for $C_{20}H_{30}$, M^+ = 270; calcd. for $C_{20}H_{32}$, M^+ = 272). Column chromatography on 25 per cent silver nitrate-silica gel (the column was made up in hexane) afforded a single compound with R_t 5.18 min in the hexane eluent (first fraction) as shown by GLC analysis (flame) of the solution (11% QF-1 + OV-17 on 100/120 mesh GCQ column, C.T. 180°, H.F.R. 88 ml/min). The GLC-MS (11% QF-1 + OV-17 100/120 GCQ mesh column, C.T. 180°) gave the parent ion at M^+ = 272 (calc. for $C_{20}H_{32}$, M^+ = 272). Evaporation of the solvent yielded approximately 3 mg of crude white crystalline 151, m.p. 52-57°C. Due to the presence of a large amount of impurity which gave a peak at 74 cps, and lack of material, a clear NMR could not be obtained. However, there were definitely no vinyl protons present, and the only other peaks were in the methyl region (0.85-1.15 δ). The IR showed no characteristic functional groups.

The above reaction was rerun using larger quantities. A solution of 179 (500 mg) in boron trifluoride-etherate (9.0 g) which had been maintained below 0°C, was added to a solution of sodium borohydride (500 mg) in diglyme (25 ml) at -70°C. Following the given procedure, the reaction yielded a nonvolatile liquid (450 mg). GLC analysis (flame) of the liquid (11% QF-1 + OV-17 on 100/120 mesh GCQ column,

C.T. 180°, H.F.R. 88 ml/min) showed the presence of one component with R_t 10.4 min (11% starting material by GLC comparison with known sample) and seven other products with R_t 1.1, 4.8, 5.3, 5.8, 6.1, 6.9 min (7:15:18:11:27:2:9 %). Column chromatography on 40 g of 25% silver nitrate-silica gel (the column was made up in hexane) afforded a solution which contained one major component with R_t 5.8 min (75%) and one minor product with R_t 8.8 min (25%). Evaporation of the solvent yielded 75 mg of crude 151 in the form of crude nonvolatile liquid; ν_{max}^{film} 2800-3000 cm^{-1}; NMR ($CHCl_3$):δ 0.81(3H), 0.86(6H), 0.92(3H). There was a large peak at 72 cps due to some impurity, as well as other minor peaks in the methyl region, which were probably due to the minor product which was present (25%). An attempt was made to separate the impurities using preparative TLC under the following sets of conditions:

Sorbent	Liquid Phase
silica gel-TLC-7G	hexane
silica gel-TLC-7G	acetone
silanized silica gel - FH_{254}	acetone

When each plate was cut into approximately eight fractions, removed, and washed with chloroform no separation was obtained. When an attempt was made to remove the starting material from the silanized silica gel by the normal procedure (washing with chloroform) very little starting material was recovered. The silanized silica gel was placed in a soxhlet and continuously extracted with chloroform. GLC analysis (flame) of the chloroform solution (11% QF-1 + OV-17 on 100/

120 mesh column, C.T. 180°, H.F.R. 88 ml/min) showed no peak which corresponded to compound 151, isotrachylobane. However, there was one new peak with R_t 5.4 min (15%). The remaining material was a very complex mixture of components with very short retention times. The chloroform was evaporated *in vacuo* to yield a yellow nonvolatile liquid (~ 50 mg). The NMR spectrum in deutero-chloroform of this crude mixture showed the presence of vinyl protons at 5.0-5.8 δ.

The above reaction was rerun under the same conditions. However, all solvents used during the reaction had been doubly distilled in an attempt to eliminate the impurity which gives a signal at 74 cps in the NMR spectrum. After completion of the reaction, column chromatography of the resulting product on 25 per cent silver nitrate-silica gel afforded impure 151 (50 mg). GLC analysis showed the presence of one major compound and one minor compound with the same retention times and ratios as described above. The infrared spectrum of 151 showed no characteristic functional groups. The NMR spectrum ($CDCl_3$) of 151 showed signals at δ 0.65 (1H, d, J = 2 cps), 0.81 (3), 0.86 (6H), 0.92 (3H). There was a complete absence of any signals in the vinyl region and there was no peak at 74 cps which had been present in all of the other spectra. There were some small peaks in the methyl region which were due to the minor compound (25%). The mass spectrum of 151 gave the parent peak at m/e 272. The precise mass determination of M_{272} using 1,1,2,2-tetrabromoethane as the reference compound gave M_{272} = 272.261; the molecular weight calculated for $C_{20}H_{32}$ was M_{272} = 272.250.

GLC-MS analysis (11% QF-1 + OV-17 on 100/120 mesh, C.T. 180°) of the minor substituent showed a parent ion at m/e = 272.

CHAPTER VII

DISCUSSION OF RESULTS CONCERNING THE SYNTHESIS OF ISOTRACHYLOBANE

The goal of this portion of the thesis was to complete the synthesis of isotrachylobane utilizing intermediate 179 which had been previously synthesized, in this laboratory, by procedures[87] given in the introduction. It was thought that if reaction conditions (temperature, time, reagents, etc.) were varied, persistently, intermediate 179 should yield isotrachylobane.

An initial experiment was carried out in this laboratory by Chetty[41] in which he treated intermediate 179 with boron trifluoride-etherate and sodium borohydride under the same conditions as those described by Herz[81] and co-workers when they reported the synthesis of methyl *anti*-trachylobanate *via* a similar intermediate. GLC-MS analysis of the major product obtained under these conditions showed it to be the same rearrangement product (182) which had been obtained previously by Gabriel.

Since dehydration and rearrangement had been the major problem encountered in the attempted cyclization of intermediate 179, a modification was used in which the boron trifluoride-etherate was cooled in a dry ice-acetone bath before adding 179. However GLC-MS analysis showed the major product (84%) to be compound 182.

Since the tertiary alcohol in compound 174 had been dehydrating before participation by the double bond, compound 179 was treated only with lithium aluminum hydride at various temperatures. It was thought that the tertiary alcohol might still be a good leaving group and allow participation of the double bond. However, GLC analysis indicated that no reaction had occurred. These results showed that a complexing agent is needed for cyclization of tertiary alcohol (179).

Reactions carried out by Gabriel[87] using mixed hydride systems at reflux temperatures in di-n-butyl ether had not been successful in yielding isotrachylobane. However it was thought that these systems might be successful if the reactions were carried out at lower temperatures. GLC analysis showed that overnight treatment of 179 with lithium aluminum hydride and aluminum chloride (2:1) at room temperature gave only starting material. The same result was obtained by subsequent treatment with the same reagents at 100°C.

Treatment of 179 with lithium aluminum hydride and aluminum chloride (1:1) in dioxane gave only starting material according to GLC analysis. However when 179 was treated with the same reagents at 100°C for three days one major product was obtained. The product was shown to be identical to compound 184 by NMR and GLC-MS comparison. This product must have arisen by dehydration of 179.

When 179 was treated overnight with lithium aluminum hydride and aluminum chloride (1:3) at room temperature, GLC analysis showed that no reaction had occurred. The reaction was rerun by treating an additional amount of 179 with a large excess of lithium aluminum hydride and aluminum chloride (1:3) for ten minutes at room temperature. A

mixture was obtained which contained one major product (53%) according to GLC analysis. Column chromatography gave the major product, which was shown to have the same retention time as compound 179, in the chloroform eluent.

Since the mixed hydride systems failed, attention was again focused on the boron trifluoride-etherate system. It was thought that reverse addition of the reagents might give the desired product. Accordingly, tertiary alcohol 179 was dissolved in dioxane containing sodium borohydride. Boron trifluoride-etherate was added to this mixture and allowed to remain overnight at room temperature. Work-up yielded one product which showed the same NMR spectrum and GLC retention time, as compound 184. Therefore, under these conditions, dehydration takes place readily.

Because of the dehydration problem, it was decided that 179 should be reacted with sodium borohydride and boron trifluoride-etherate at extremely low temperatures. The reaction was carried out by addition of 179 to boron trifluoride-etherate which had been cooled to -70°C in a dry ice-acetone bath. After allowing the mixture to warm, until compound 179 dissolved, it was added to a mixture of sodium borohydride in diglyme which had been cooled to -70°C. After allowing the reaction mixture to warm to 0°C, GLC analysis showed the presence of starting material (66%) and six products in the ratio 6:9:4:7:3:5. GLC-MS analysis of the last five products in the order listed gave parent ions at M^+ = 272, 272, 272, 270, 270. Since the first three compounds show a parent ion at M^+ = 272, they must contain an additional ring, as found in isotrachylobane, or one double bond. The two compounds

giving parent ions at M^+ = 270 are probably dehydration products which contain two double bonds as in 183 and 184.

It was thought that elution of this mixture with hexane on a silver nitrate-silica gel column should give, in the first few fractions, only those compounds containing no double bonds. Should the hexane eluent contain a compound with a parent ion at M^+ = 272, mechanistic considerations would lead one to assign the structure as isotrachylobane.

Column chromatography on 25% silver nitrate-silica gel gave mainly compound 151, m.p. 52-57°C, in the first fraction of the hexane eluent. The GLC-MS gave the parent ion at M^+ = 272 (calc. for $C_{20}H_{32}$, M^+ = 272). Due to the presence of a large amount of impurity which gave a peak at 74 cps, and the small amount of material, a clear NMR could not be obtained. However there were definitely no vinyl protons present and the only other peaks were in the methyl region (0.85-1.15 δ). The IR showed no characteristic functional groups.

When the reaction was rerun using larger quantities of material, and separated as above on a 25% silver nitrate-silica gel column, a mixture was obtained in the first fraction of the hexane eluent, which contained compound 151 as the major product (75%). The minor compound (25%), which had not been present in the previous reaction, had a longer retention time. The IR showed no functinal groups. The NMR showed the presence of three methyl groups at 0.81, 0.86, and 0.92 δ. There was an extremely large peak at 74 cps which was due to some long chain hydrocarbon material present in the solvents used. There were small peaks present in the methyl region which were due to the presence of the minor component.

An attempt was made to eliminate the impurities by using preparative TLC with various sorbents and liquid phases. During an attempt to remove the material from silanized silica gel by heating with chloroform in a soxhlet, a mixture was recovered which contained none of the desired compound, 151. GLC analysis showed one new peak which had a slightly shorter retention time than compound 151. It was thought that this might be a rearrangement product containing one double bond. The chromatogram also showed a very complex mixture of compounds with very short retention times. When an NMR spectrum was taken of this crude mixture there were vinyl protons in the region 5.0-5.8 δ. The fact that rearrangement occurs in acidic medium to give compounds containing vinyl protons is also good evidence for the isotrachylobane structure being assigned to the major product.

The reaction was rerun again under the same conditions. However all solvents used during the reaction had been doubly distilled in an attempt to eliminate the impurity which gives a signal at 74 cps in the NMR spectrum. Separation by the usual method yielded compound 151 and the minor product in the same ratios as mentioned previously. The NMR spectrum showed a one proton signal at 0.65 δ (assigned to one of the three-membered ring protons), and four methyl groups at 0.81, 0.86 (two methyl groups), and 0.92 δ. There was a complete absence of any signals in the vinyl region. There was also a complete absence of the impurity which had given a peak at 74 cps. There were small peaks present in the methyl region which were due to the minor compound (25%). The mass spectrum of the major component of impure 151 gave the parent peak at

M^+ = 272. Precise mass determination of M_{272} gave the molecular formula as $C_{20}H_{32}$ (calcd. for 151, $C_{20}H_{32}$).

GLC-MS analysis of the minor compound (all attempts to separate it from compound 151 failed) gave the parent ion at M^+ = 272. Since there were no vinyl protons present in the NMR spectrum of the mixture, the minor product must contain either a tetrasubstituted double bond or have a structure similar to 151 in which the methyl group has migrated.

CHAPTER VIII

CONTENT OF THE ROOTS OF *SARRACENIA FLAVA*[*]

Introduction

Investigation of the content of *Sarracenia flava* (Golden Trumpet), which is indigenous to the Okefenokee Swamp in southeastern Georgia, was of interest because of the use of the ethanol extract of the roots as a home remedy for a variety of illnesses.

Preliminary investigations by Gabriel,[87] in which he sent the crude methanol extract to the National Cancer Institute for testing, showed that the extract did have anti-tumor activity.

Efforts were then concentrated on the isolation of the compounds responsible for the activity using a scheme recommended by the National Cancer Institute.

Experimental

Extraction Procedure

The dry ground roots (4400 g) of *Sarracenia flava* were extracted with n-hexane (24 liters) for six days in a continuous extractor. The n-hexane solution was removed from the extractor and evaporated *in vacuo* to yield 360 g of crude hexane extract (fraction I). The plant material was extracted with 95% ethanol (24 liters) for six days. Evaporation of the ethanol solution *in vacuo* yielded approximately 700 g

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[*]This work was accomplished with the assistance of E. Stamatakis.

of crude extract which was distributed between chloroform and water using a liquid-liquid extractor. Evaporation *in vacuo* of the chloroform layer gave approximately 599 g of crude material (fraction II). The aqueous layer was concentrated by using freeze-drying techniques to give 100 g of a crude reddish syrup (fraction III). Fraction III was extracted with a chloroform-methanol (2:1) solution. Evaporation of the chloroform-methanol solvent system gave 86 g of crude material (fraction IV). The insoluble portion (15g) was labeled as fraction V. Fractions I-V (5g) were sent to the National Cancer Institute for testing.

Investigation of Fraction II

A portion (100 g) of the chloroform soluble fraction (II) was equilibrated between chloroform and 5 per cent aqueous sodium hydroxide. A large amount (42 g) of a beige solid (fraction VI), which was not soluble in either layer was filtered from the solution. The chloroform layer was washed with water and evaporated *in vacuo* to yield 7 g of dark green material (fraction VII). The basic solution was acidified with hydrochloric acid and extracted with chloroform. The chloroform extract was washed with water, dried over anhydrous magnesium sulfate, and evaporated *in vacuo* to yield 0.9 g of a dark gummy material (fraction VIII).

Investigation of Fraction VI

The beige solid was recrystallized from hot methanol and acetone to yield a white crystalline material (compound *A*) which did not melt when heated to 315°C. ν_{max}^{KBr} 3300 cm^{-1} (strong), 1630 cm^{-1} (weak),

1550 cm^{-1} (strong), and 875 cm^{-1} (medium); NMR ($CDCl_3$): δ 0.87 (3H,S) 1.02 (3H, S) 1.12 (6H, S), 1.22 (3H, S), 1.82 (3H, S), 4.83 (2H, d, J = 10 cps), 5.12 (6H, S), 7.21 (1H, S), 8.64 (1H, S). The absorption at δ 5.12 shifted to δ 5.44 upon addition of D_2O. The mass spectrum failed to show a discernible parent ion.

Compound A (200 mg) was dissolved in 3 ml of dry pyridine and 2 ml of acetic anhydride. The mixture was allowed to stir at room temperature for 36 hours. The solution was poured into ether (75 ml) and extracted four times with cold water (50 ml). The ether layer was dried over anhydrous magnesium sulfate and evaporated *in vacuo* to yield 210 mg of a white crystalline solid (compound B), m.p. 286-299°C. The infrared showed: ν_{max}^{KBr} 1725 cm^{-1}, 1680 cm^{-1}, 1630 cm^{-1}, 1240 cm^{-1}, and 875 cm^{-1}. The NMR ($CDCl_3$) spectrum showed signals at δ 0.83 (9H, S), 0.93 (3H, S), 0.97 (3H, S), 1.69 (3H, S), 2.01 (3H, S), 4.70 (2H, D, J = 7 cps). The mass spectrum gave a parent ion at M^+ = 498. A structure could not be assigned to this compound.

Investigation of Fraction VII

Fraction VII (7g) was chromatographed on a neutral alumina column (350 g, activity II). Fractions 6-8 (eluted with 40 per cent benzene-hexane) were combined to yield an extremely pure white crystalline compound (compound C), m.p. 126-128°C, $[\alpha]_D^{25°}$ = +131.5 (in $CDCl_3$). The infrared spectrum showed: ν_{max}^{KBr} 1700 cm^{-1}, 1600 cm^{-1}. The NMR ($CDCl_3$) spectrum gave absorptions at δ 0.97 (3H, S), 1.19 (3H, S), 3.58 (3H, S), 3.68 (3H, S), 6.92 (3H, M). The mass spectrum gave a parent ion at M^+ = 302 (calcd. for $C_{19}H_{26}O_3$; M^+ = 302). Compound C was shown to be identical with authentic methyl-o-methyl podocarpate

(80) m.p. 128°C, $[\alpha]_D^{25°}$ = +131 (in $CDCl_3$), which had been previously prepared in this laboratory from podocarpic acid (53), by direct comparison of the physical and spectra properties.

Fraction 23 (eluted in chloroform) gave a white crystalline solid (compound D), m.p. 214-217 C, $[\alpha]_D^{25°}$ (in pyridine). The infrared (KBr pellet) spectrum showed 3300 cm^{-1}, 1630 cm^{-1}, 875 cm^{-1}. The NMR ($CDCl_3$) showed absorptions at δ 0.76 (3H, S), 0.84 (3H, S), 0.84 (3H, S), 0.99 (3H, S), 1.02 (3H, S), 1.05 (3H, S), 1.71 (3H, S), 3.58 (2H, d of d, J = 11 cps), 4.67 (2H, d, J = 5 cps). The mass spectrum gave a parent ion at M^+ = 442 (calcd. for $C_{30}H_{50}O_2$; M^+ = 442). The precise mass determination using PFA as the standard gave M^+ = 442.3745 (calcd. M^+ = 442.3811).

Investigation of Fraction VIII

Fraction VIII (0.9 g) was chromatographed on silica gel. The 15th fractin (eluted with 30% benzene-chloroform) gave a crude crystalline material which showed three spots at R_f 0.60, 0.32, 0.05 on a TLC plate. Preparative TLC was attempted using silica gel as the sorbent 5 per cent acetone-10 per cent benzene-85 per cent chloroform as the liquid phase. The plate was cut into five fractions. When the third fraction was washed with chloroform, which was removed *in vacuo*, 11.8 mg of a white crystalline material (compound E), m.p. 110-112°C, was obtained. The infrared spectrum showed: ν_{max}^{KBr} 3300 cm^{-1}, 1660 cm^{-1}, 1570 cm^{-1}, 1515 cm^{-1}, 1280 cm^{-1}. The NMR ($CDCl_3$) spectrum showed absorptions at δ 2.53 (3H, S), 3.94 (3H, S), 6.15 (1H, b.s.), 7.25 (3H, M). The mass spectrum gave a parent ion at M^+ = 166 (calcd. for $C_9H_{10}O_3$; M^+ = 166). Direct comparison of the NMR spectrum of compound

E with that of acetovanillon[92] (185), m.p. 115°C,[93] showed the two compounds to be identical.

Attempted Confirmation of the Presence of Methyl-O-Methyl Podocarpate (80)

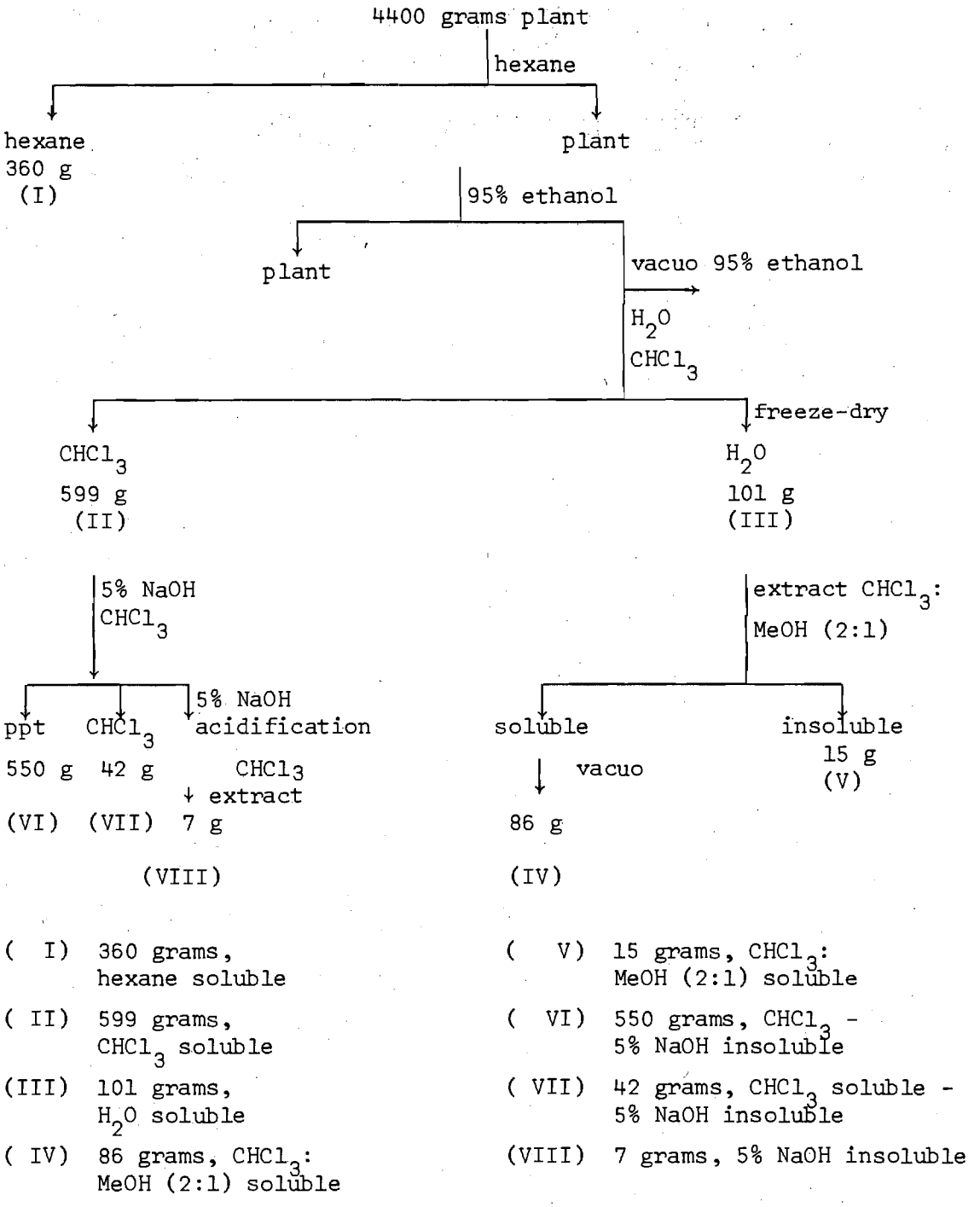
When a freshly collected sample (May, 1969) of *Sarracenia flava* was extracted as previously described, the presence of methyl-o-methyl podocarpate in the corresponding fraction II could not be found by GLC-MS analysis.

Results and Discussion

The powdered roots of *Sarracenia flava*, after defatting with n-hexane, were extracted with 95 per cent ethanol (see Figure 12 for standard fractionation procedure). After evaporating the solvent *in vacuo*, the residue was equilibrated between chloroform and water. The water-soluble material was extracted with chloroform-methanol (2:1) solution to give soluble (IV) and insoluble (V) fractions. The chloroform soluble material (II) was extracted with 5 per cent aqueous sodium hydroxide to remove any acidic material. A beige solid (VI) that was not soluble in either layer, was filtered from the mixture. The chloroform soluble portion was labeled as fraction VII and the acidic material as fraction VIII. Tests for anti-tumor activity were performed by the National Cancer Institute on fractions I-VI. Most of the activity was shown to be located in fractions II and V, with somewhat less in fraction VI.

Recrystallization of VI from methanol-acetone solution gave a white solid which, upon heating to 315°C, did not melt. The infrared spectrum showed absorptions for an alcohol (3300 cm^{-1}), two double bonds

Sarracenia flava



(I) 360 grams, hexane soluble

(II) 599 grams, $CHCl_3$ soluble

(III) 101 grams, H_2O soluble

(IV) 86 grams, $CHCl_3$: MeOH (2:1) soluble

(V) 15 grams, $CHCl_3$: MeOH (2:1) soluble

(VI) 550 grams, $CHCl_3$ - 5% NaOH insoluble

(VII) 42 grams, $CHCl_3$ soluble - 5% NaOH insoluble

(VIII) 7 grams, 5% NaOH insoluble

Figure 13. Standard Fractionation Procedure

(1630 cm^{-1}, 1600 cm^{-1}), and an absorption for an exocyclic double bond (875 cm^{-1}). There was also a strong absorption at 1550 cm^{-1}. The NMR spectrum gave absorptions for five tertiary methyl groups (δ 0.87, 1.02, 1.12, 1.22), possibly a methyl on a double bond (δ 1.82), and an exocyclic double bond (δ 4.83). The other absorptions in the NMR spectrum (δ 5.12, 7.21, 8.64) could not be assigned. The mass spectrum failed to give a discernible parent ion.

In order to aid in the elucidation of its structure, Compound A was acetylated to give compound B, m.p. 286-288°C. The infrared spectrum had absorptions for two carbonyls (1725 cm^{-1}, 1680 cm^{-1}), an acetate group (1240 cm^{-1}), and an exocyclic double bond (875 cm^{-1}). The NMR spectrum gave absorptions for five tertiary methyl groups (δ 0.83, 0.93, 0.97), possibly a methyl on a double bond (δ 1.69), an acetate group (δ 2.01) and a doublet (J = 7 cps) for an exocyclic double bond (δ 4.68). The mass spectrum gave a parent ion at M^+ = 498. Although a structure could not be assigned to compounds A and B, it was thought that they were triterpenes containing one isopropenyl and at least one hydroxyl group which was acetylated in the case of compound B.

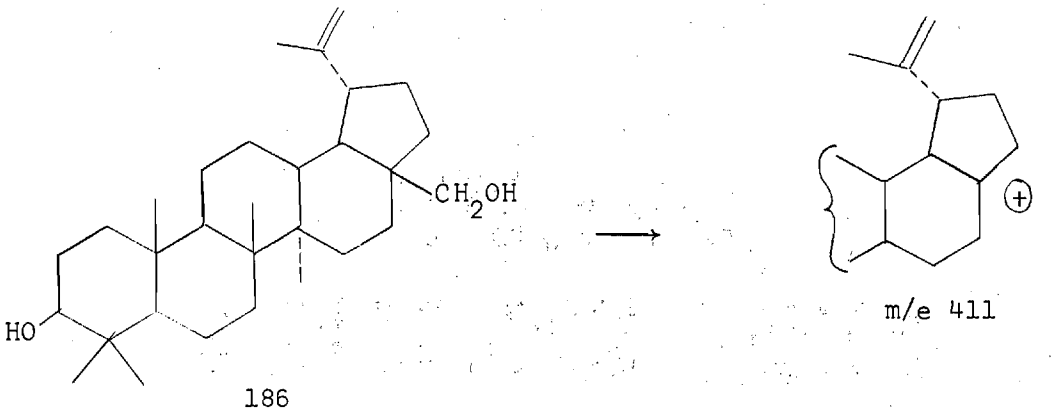
Isolation of the components in fraction VII was attempted by chromatography on neutral alumina. A crystalline compound (compound C), m.p. 127-128°C, was obtained in the 40 per cent benzene-hexane eluent. The infrared spectrum gave absorptions for an ester (1700 cm^{-1}) and an aromatic ring (1600 cm^{-1}). The NMR spectrum gave absorptions for two tertiary methyl groups (δ 1.97, 1.19), two methoxy groups (δ 3.58, 3.68), and a complex multiplet in the aromatic region (δ 6.92). The mass spectrum gave a parent ion at M^+ = 302. Compound C was shown

to be identical with methyl-o-methyl podocarpate (80) by direct comparison (m.p., IR, NMR, MS).

Since there was some question concerning the actual presence of methyl-o-methyl podocarpate in this plant, the previously described isolation procedure was repeated on some *Sarracenia flava* collected recently (May, 1969). No trace of a compound, corresponding to methyl-o-methyl podocarpate (80), could be found. It is possible that some synthetic methyl-o-methyl podocarpate (80) might have fortuitously been placed in one of the vessels containing plant material or plant extract. However, it is not known how this could have occurred.

Another white crystalline solid (compound D), m.p. 214-217°C, $[\alpha]_D^{25°}$ = +34.8 (in pyridine), was isolated in the 100 per cent chloroform eluent from the chromatography of fraction VII. The infrared spectrum showed absorptions for an alcohol (3300 cm^{-1}), and an exocyclic double bond (1630 cm^{-1}, 875 cm^{-1}). The NMR spectrum gave absorptions for five tertiary methyl groups (δ 0.75, 0.84, 0.99, 1.03), a methyl on a double bond (δ 1.82), two methylene protons next to a hydroxyl group (δ 3.61, d of d, J = 11 cps), and an exocyclic double bond (δ 4.68, d, J = 7 cps). The mass spectrum showed a parent ion at M^+ = 442 (calcd. for $C_{30}H_{50}O_2$; M^+ = 442). Precise mass determination gave M^+ = 442.3745 (calcd. M^+ = 442.3811). It was thought that the base peak at m/e 411 could easily correspond to the loss of the hydroxymethylene group. The spectra properties and the fragmentation in the mass spectrum suggested that compound D was a triterpene that was very similar to betulin (186),[94] m.p. 252-253°C.

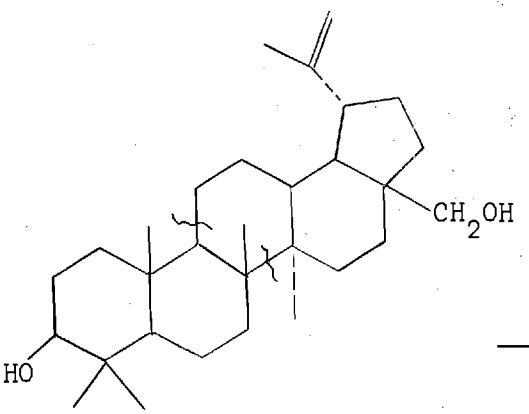
A sample of compound D was sent to R. Hale* for a mass spectra comparison with betulin (186). Both samples were run on the MS-9 at 70 and 12 electron, volts by direct insertion. The fragmentation involved principally the C-ring and the assignments made were those reported in Djerassi's book.[95] The comparison showed that the structure of betulin (186) fit the unknown compound D very well. The M/e 411 peak was assigned to loss of the hydroxymethylene group.



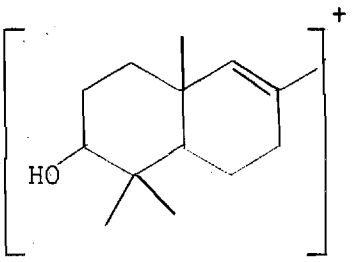
186

The cleavage shown on the following page could lead to the major fragments.

*R. Hale is a NIH Postdoctoral Fellow with Dr. Carl Djerassi at Stanford University.

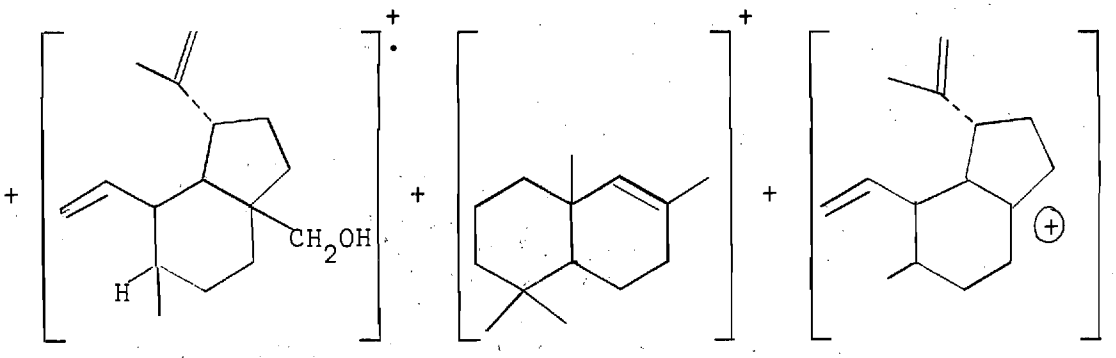


186



187

m/e 208-H• = 207



188

m/e 234

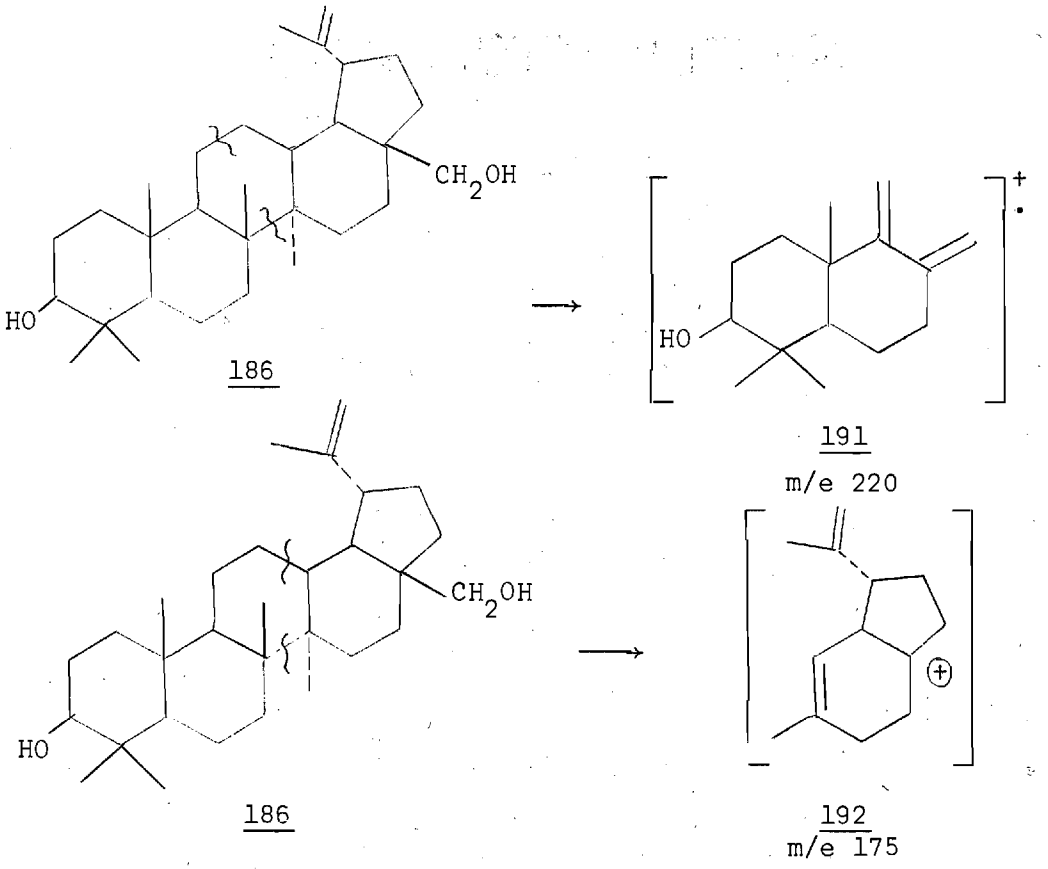
189

m/e 189

190

m/e 203

Other significant cleavages are those leading to m/e 220 and 175.

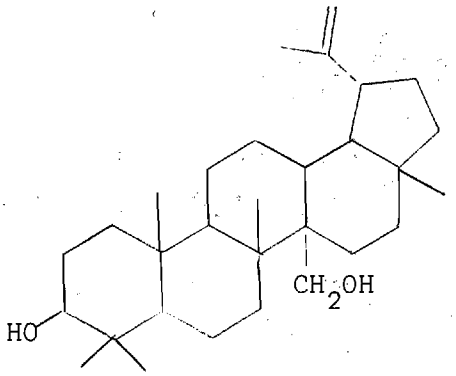


A table showing the relative intensity of these fragments in the unknown D and betulin (186) is shown below:

Table 3. Relative Intensity of Betulin (186) and Compound D

m/e	Betulin (70ev)	Compound D (70 ev)	Be (12)	D (12)
442	11	36	37	63
411	40	55	100	100
234	14	37	36	69
220	15	20	36	30
207	57	59	99	80
203	55	100	79	98
189	100	80	82	43
175	40	31	10	10

Since small errors in the operating voltage were not significant in the 70 ev spectra, it was better to consider these spectra. The most noticeable differences were in the fragments (m/e 234 and 203) coming from the D and E rings which contained the hydroxymethylene group. The identical fragmentation patterns seemed to eliminate any major structural differences. The difference in melting points (betulin, 252-253° C;[94] compound D, 214-217°C) as well as the differences in the peaks at m/e 234 and 203, led Hale[96] to speculate that the difference in the compounds was in the location of the 1° hydroxyl group rather than the 2° hydroxyl group. It is possible that a structure such as 193 would give a fragmentation pattern identical to that of betulin (186). There are a number of possible structures consistent with the biogenetic theory.



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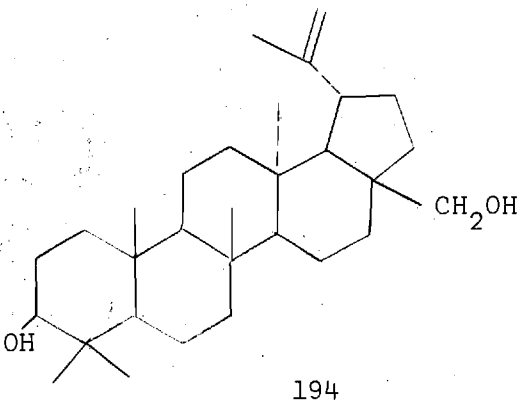

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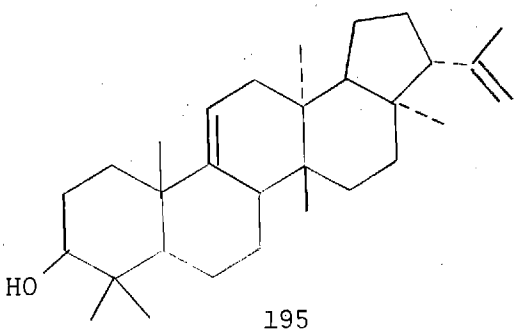

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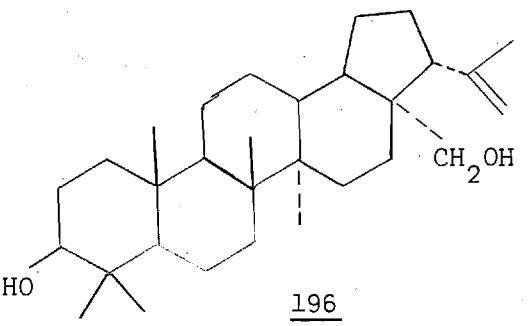

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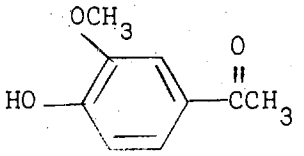
One possibility is a simple inversion of configuration of the isopropenyl, hydroxymethylene, or C-14 angular methyl groups. Also possible is the migration of the latter two, but such a migration would have to be limited to the D and E rings since the mass spectrum shows that there is an angular methyl group at C-8. Thus another possibility is 194 or variations on it. A structure having the D and E rings of fernene (195) without the migration of the C-8 and C-14 methyls as in 196 is also possible. All of these possibilities are of biogenetic interest.

The 5 per cent aqueous sodium hydroxide layer (fraction VIII) was acidified and extracted with chloroform. The residue from the chloroform layer was chromatographed on silica gel. Elution with 30 per cent benzene-chloroform gave a crude semi-crystalline material. Separation by preparative TLC gave a small amount of a white crystalline solid (compound E), m.p. 110-112°C. The infrared spectrum gave absorptions for a hydroxyl group (3300 cm^{-1}), a carbonyl group (1660 cm^{-1}), and an aromatic ring (1570 cm^{-1}, 1515 cm^{-1}). The NMR spectrum showed absorptions for a methyl next to a carbonyl (δ 2.53), a methoxy group (δ 3.94), one hydroxyl group (δ 6.15), and three aromatic protons (δ 7.25, m). The mass spectrum gave a parent ion at M^+ = 166 (calcd. for $C_9H_{10}O_3$; M^+ = 166). The base peak at m/e 151 (M^+ - 15) correspond to loss of a methyl group. Other significant peaks were m/e 149 (M^+ - 17), corresponding to loss of OH and m/e 123 (M^+ = 43) corresponding to loss of $CH_3C{=}O$. The NMR spectrum of compound E was identical to the NMR spectrum of acetovanillan (185).[92] The other

spectra and physical properties were consistent with the acetovanillon[93] structure (185), m.p. 115°C.

Although there are a number of crystalline fractions available from this plant, no other compounds have been identified at this time.



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CHAPTER IX

CONCLUSIONS

The synthesis of intermediate lactam 123 has been accomplished, which should lead to the synthesis of dihydroajaconine, by a five-step reaction sequence.

Intermediate 179, which was synthesized previously by Gabriel, has been converted to Isotrachylobane.

Several compounds have isolated from *Sarracenia flava* (Golden Trumpet). One of the compounds has been shown to be acetovanillan (185) and another compound has been shown to have a triterpene structure similar to that of betulin (186). The crude extract has anti-tumor activity, as shown by the National Cancer Institute.

CHAPTER X

RECOMMENDATIONS

The following sequence of reactions should be performed on lactam (123) in an attempt to synthesize dihydroajaconine (6):

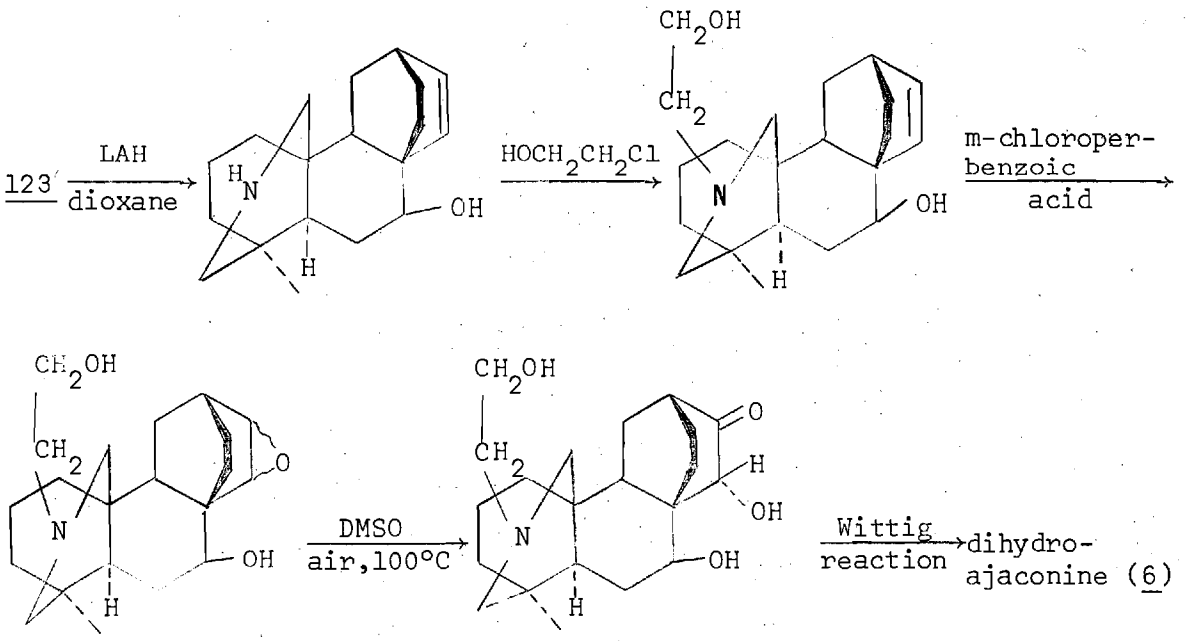

Figure 14. Proposed Scheme for the Synthesis of Dihydroajaconine (6) from Lactam (123)

Dihydroajaconine (6) can then be converted to ajaconine (1) by treatment with mercuric acetate[97] and base.[98] One approach to the total synthesis of atidine (2) would be the conversion of ajaconine (1) to atidine (2) by a rational sequence of reactions. The synthesis of ajaconine (1) would then complete the synthesis of both compounds.

Isotrachylobane should be rearranged in acid media in an attempt to interrelate the phyllocladene, isoatisirene, isohabaene, and isotrachylobane skeleta. An attempt should be made to identify the minor component which was present along with isotrachylobane.

Spectra of all of the crystalline fractions obtained from *Sarracenia flava* should be taken in order to aid in the elucidation of their structures. Degradation reactions should be performed on compound D to further elucidate its structure. Also, comparison of the NMR spectrum of compound D with that of betulin (186) might be helpful.

APPENDIX

The reported quantities for the ORD measurements[60] were calculated as shown in Equations 1-4, where α_{289} is the rotation at 289 mμ, $[\alpha]_{289}$ is the specific rotation at 253 mμ, and $[\Phi]_{289}$ is the molecular rotation at 289 mμ.

The molecular amplitude, a, is defined as the difference between the molecular rotation at the extremum (peak or trough) of the longer wavelength $[\Phi]_1$, and the molecular rotation at the extremum of shorter wavelength $[\Phi]_2$, divided by 100.

$$\alpha_{289} = (\text{instrument scale in degrees}) \times (\text{chart measurement}) \tag{1}$$

$$[\alpha]_{289} = \frac{100 \times \alpha_{289}}{\left[\text{conc. in gm/100 ml}\right] \times \left[\begin{array}{c}\text{pathlength of transmitted} \\ \text{light in dm}\end{array}\right]} \tag{2}$$

$$[\alpha]_{289} = \frac{[\alpha]_{289} \times (\text{mol. wt.})}{100} \tag{3}$$

$$a = \frac{[\Phi]_1 - [\Phi]_2}{100} \tag{4}$$

The reported quantities for the CD measurements were calculated as shown in Equation 5.

$$[\theta] = \frac{3300 \text{ (scale)} \times \text{(chart measurement)}}{\left\{\text{conc. in moles/liter}\right\} \times \left\{\begin{array}{c}\text{pathlength of transmitted} \\ \text{light in cm}\end{array}\right\}} \qquad (5)$$

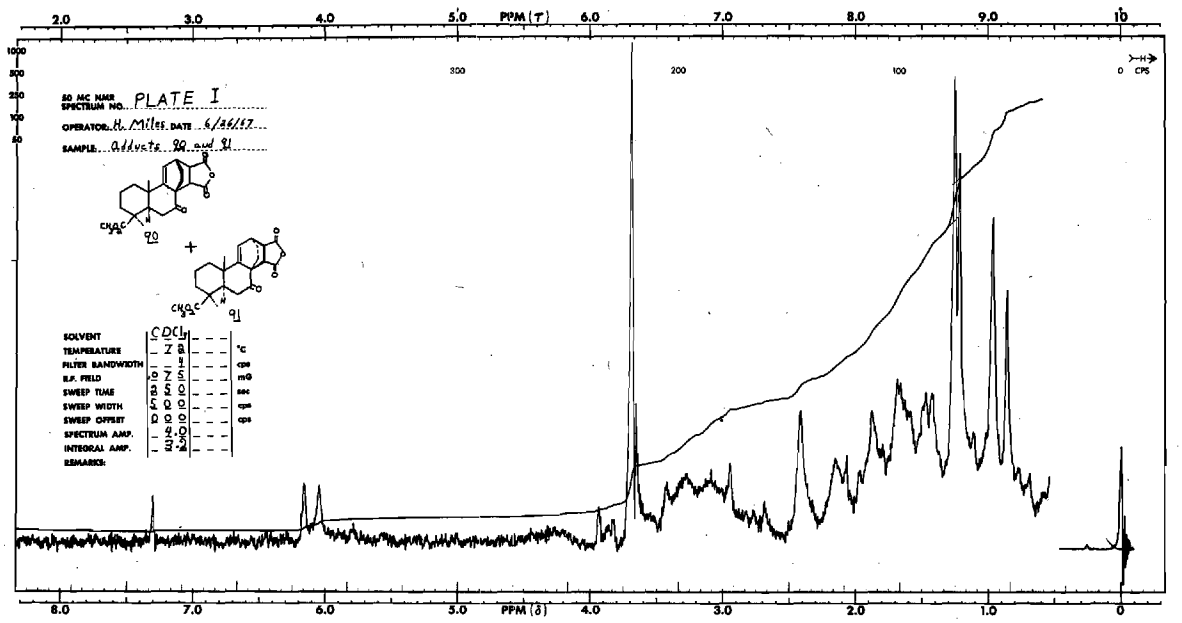

Plate I. NMR Spectrum of Adducts 90 and 91

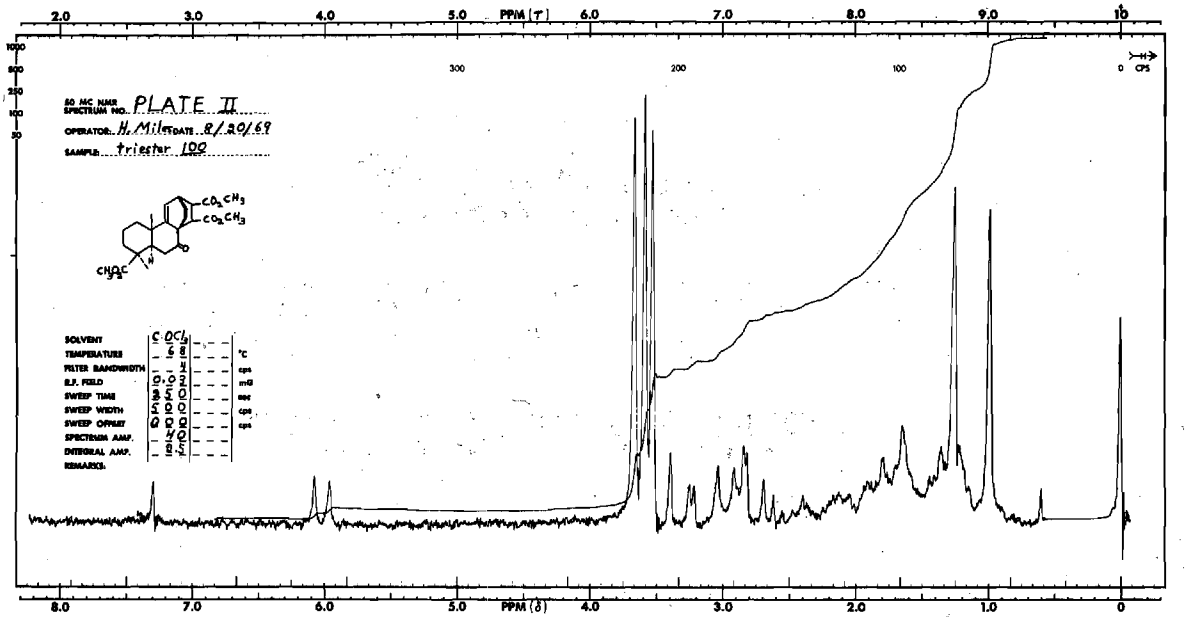

Plate II. NMR Spectrum of Triester 100

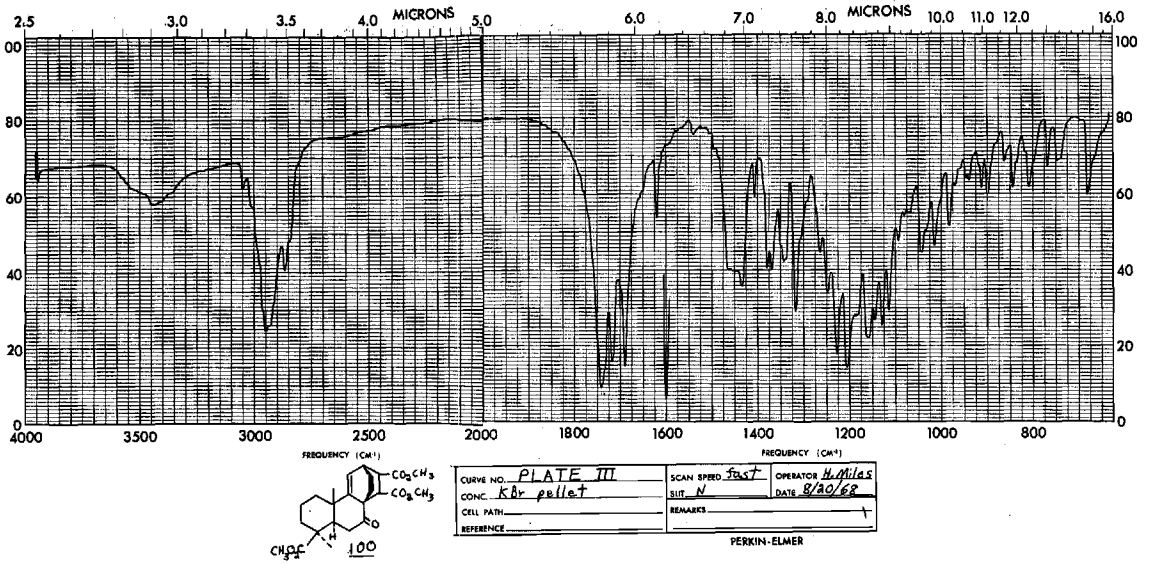

Plate III. Infrared Spectrum of Triester 100

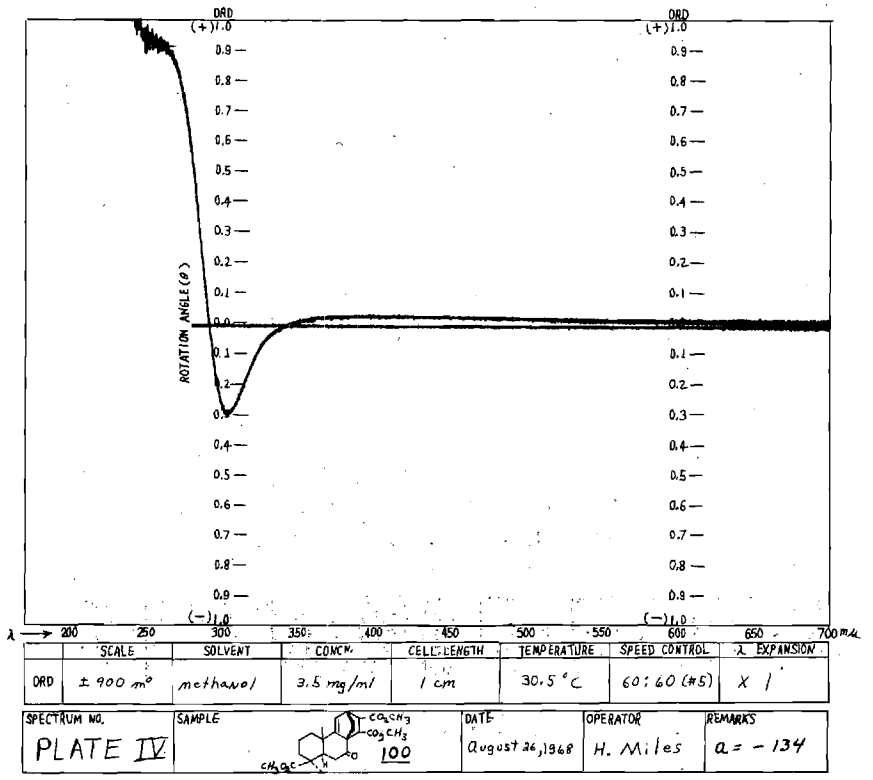

Plate IV. ORD of Triester 100

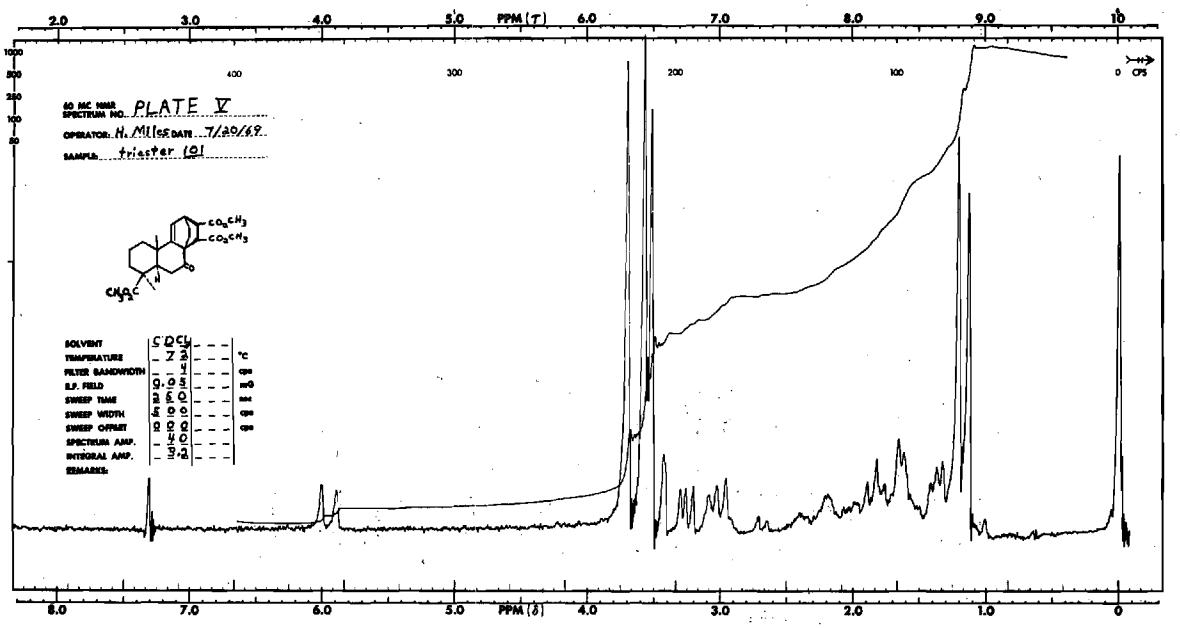

Plate V. NMR Spectrum of Triester 101

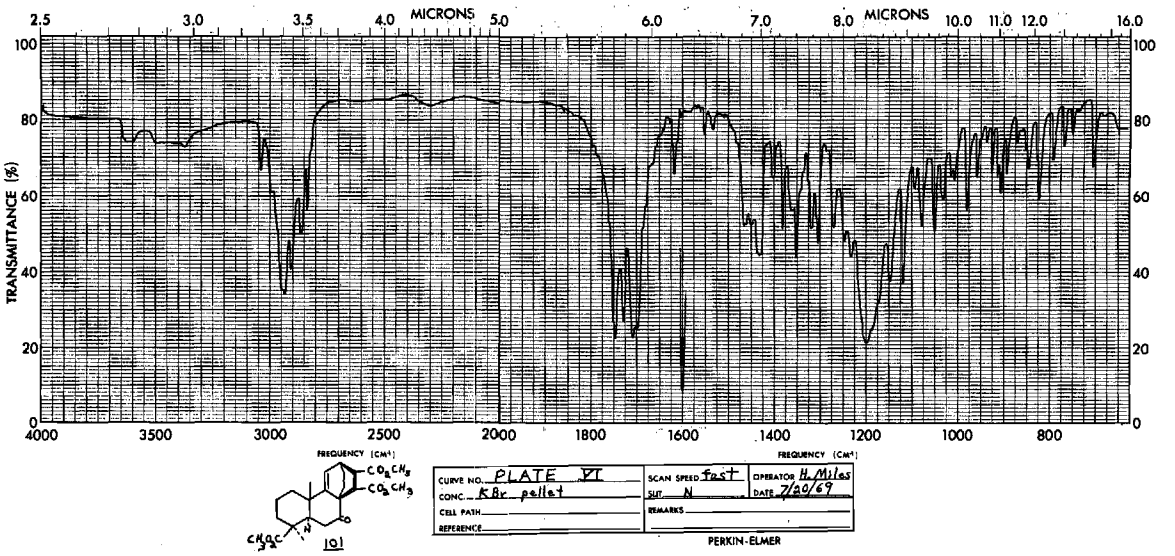

Plate VI. Infrared Spectrum of Triester 101

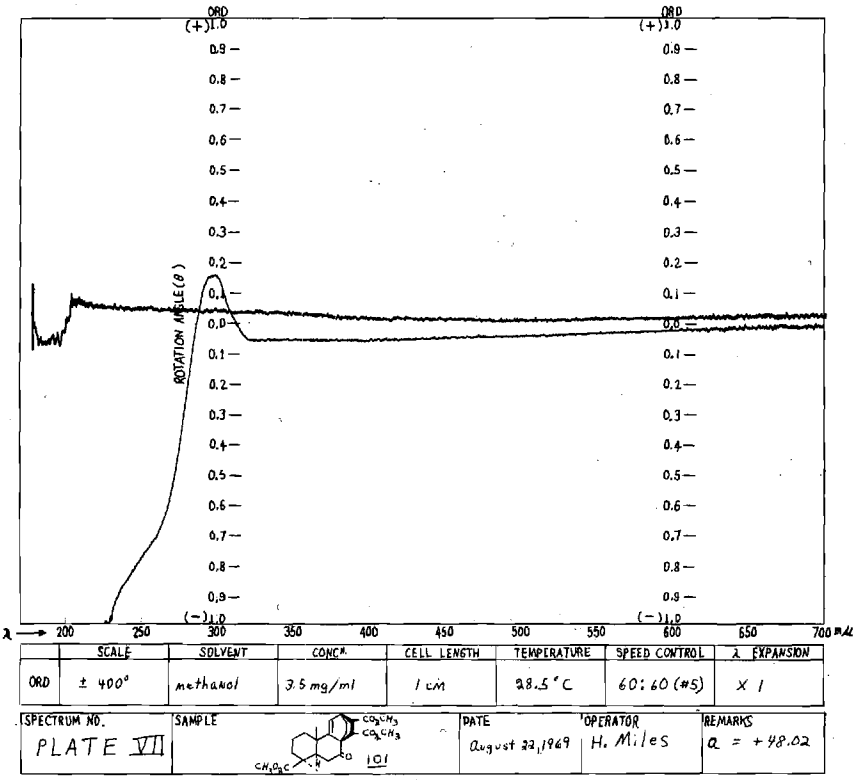

Plate VII. ORD of Triester 101

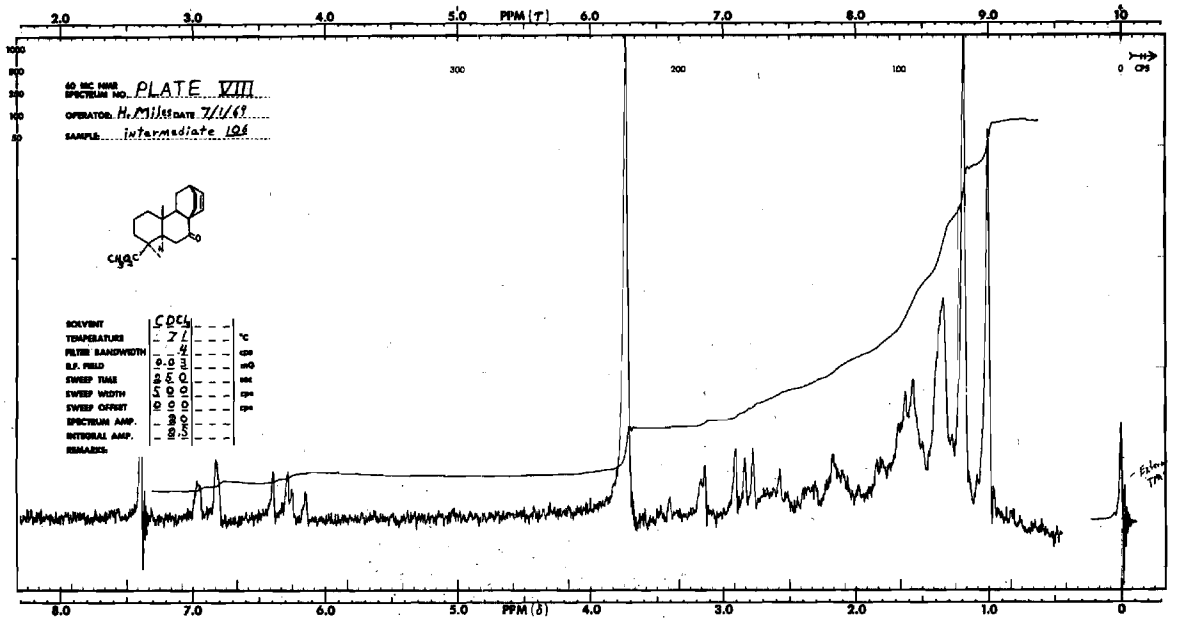

Plate VIII. NMR Spectrum of Intermediate 106

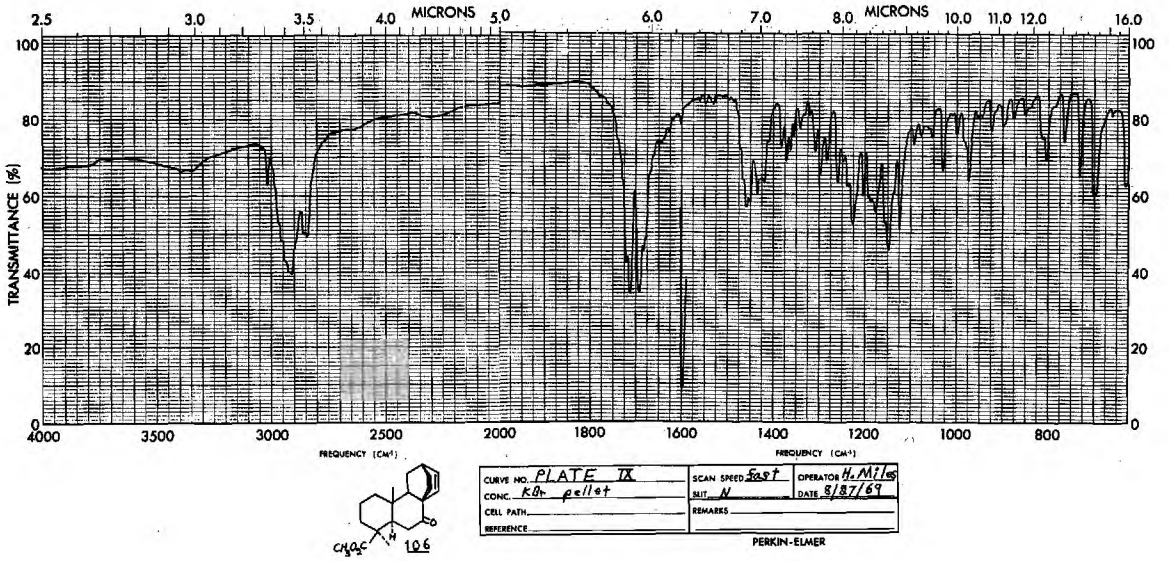

Plate IX. Infrared Spectrum of Intermediate 106

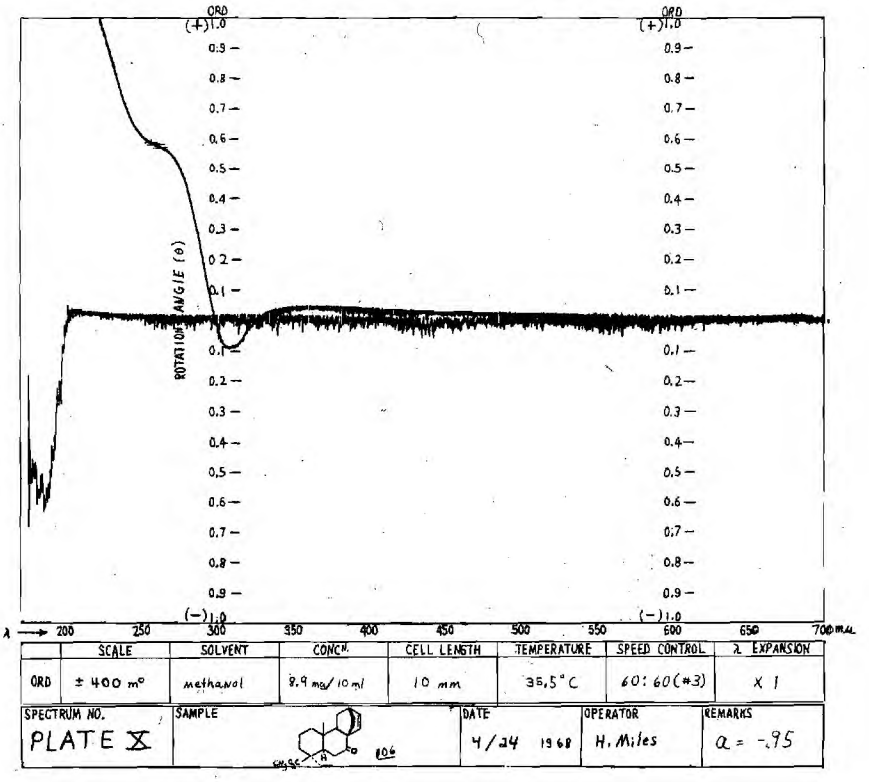

Plate X. ORD of Intermediate 106

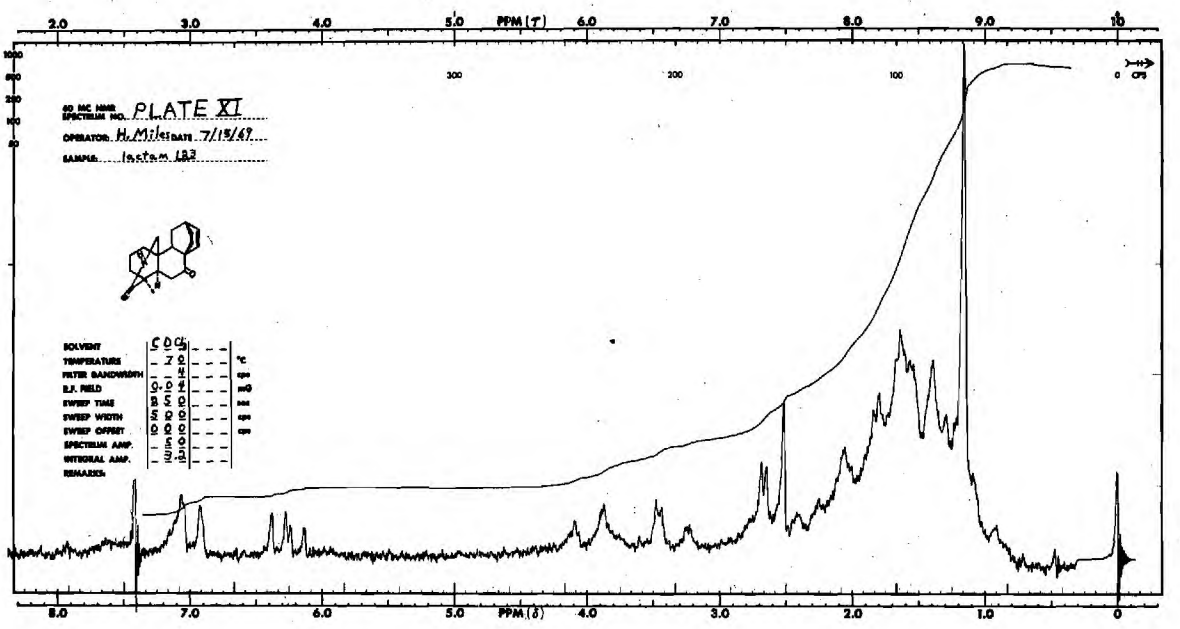

Plate XI. NMR Spectrum of Lactam 123

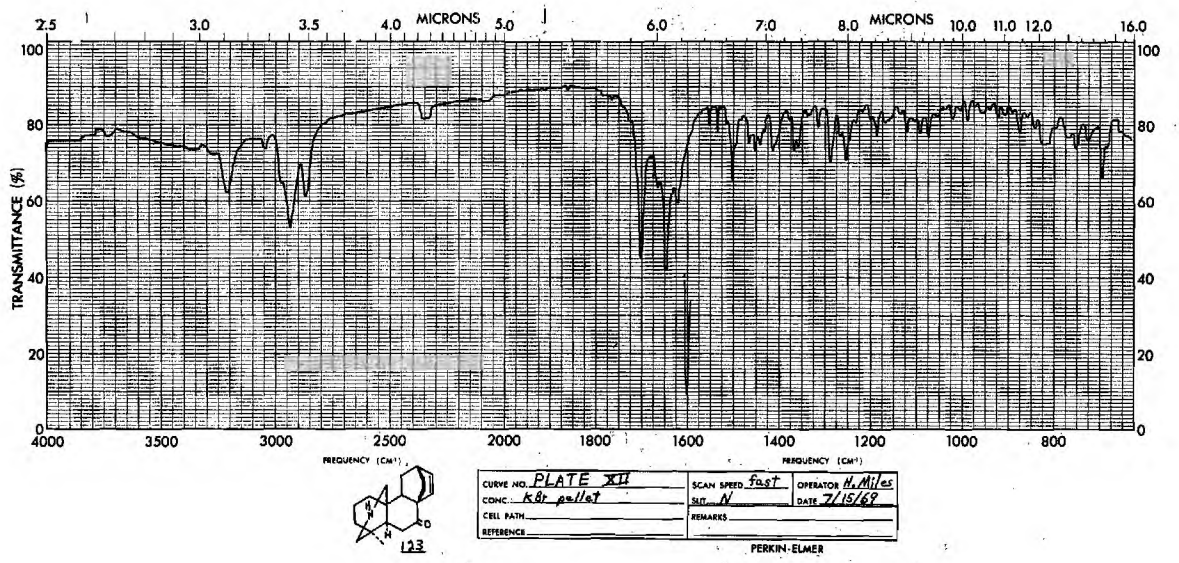

Plate XII. Infrared Spectrum of Lactam 123

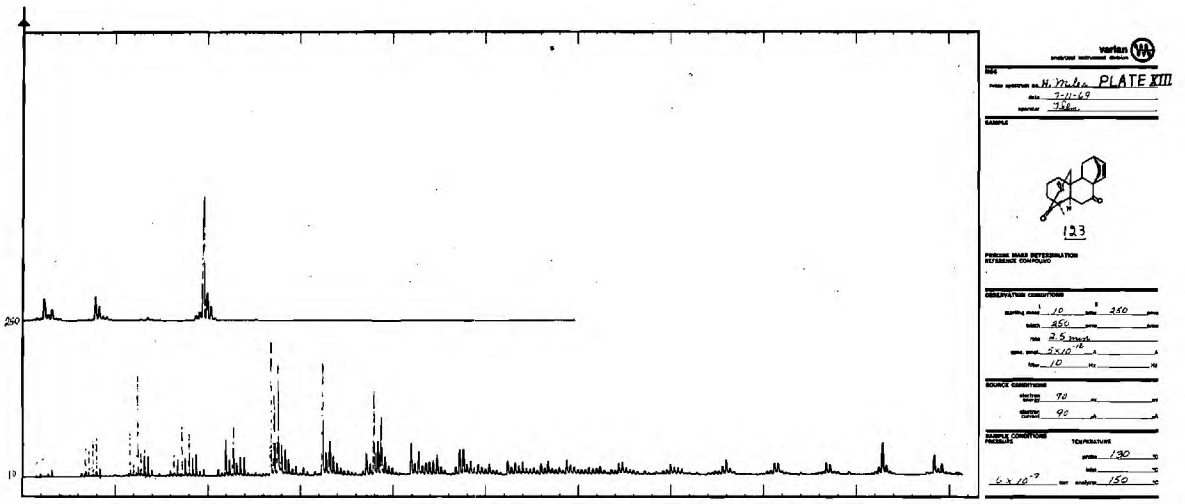

Plate XIII. Mass Spectrum of Lactam 123

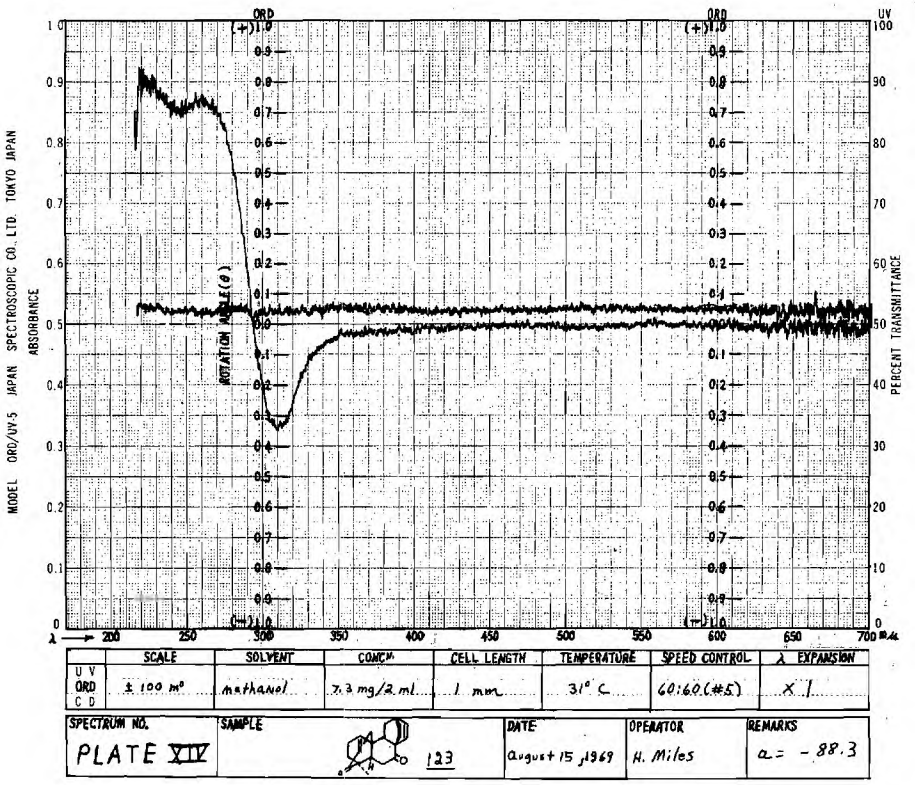

Plate XIV. ORD of Lactam 123

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