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THE UNIVERSITY OF ALBERTA

DIELS-ALDER REACTIONS OF 4,4-DIMETHYL-2-CYCLOHEXEN-1-ONES AND THEIR APPLICATION TO THE SYNTHESIS OF NATURAL PRODUCTS

by

ERIC NORMAN CRAWFORD BROWNE

A THESIS

SUBMITTED TO THE FACULTY OF GRADUATE STUDIES AND RESEARCH

IN PARTIAL FULFILMENT OF THE REQUIREMENTS FOR THE DEGREE

OF DOCTOR OF PHILOSOPHY

DEPARTMENT OF CHEMISTRY

EDMONTON, ALBERTA

SPRING, 1980

THE UNIVERSITY OF ALBERTA

FACULTY OF GRADUATE STUDIES AND RESEARCH

The undersigned certify that they have read, and recommend to the Faculty of Graduate Studies and Research, for acceptance, a thesis entitled: DIELS-ALDER REACTIONS OF 4,4-DIMETHYL-2-CYCLOHEXEN-1-ONES AND THEIR APPLICATION TO THE SYNTHESIS OF NATURAL PRODUCTS submitted by ERIC N.C. BROWNE in partial fulfilment of the requirements for the degree of Doctor of Philosophy.

Supervisor

A. G. Fallis

External Examiner

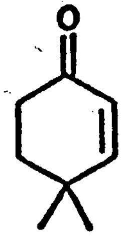
Date Feb. 7, 1980

for my parents

and the horde

Abstract

The Diels-Alder reactions of three 4,4-dimethyl-2-cyclohexen-1-ones (1, 2 and 3) were studied. Enone 1 was found to be unreactive under a variety of thermal and Lewis acid catalysed conditions. Dienone 2 was found to react slowly but in synthetically useful yields with a variety of hydrocarbon dienes under boron trifluoride etherate catalysis to give adducts of general formula 4. The adducts were produced in accordance with the normal rules governing Diels-Alder addition with one exception. The addition of isoprene to 2 proceeded exclusively to give the adduct 5 formed in violation of the *para*-rule. Adduct 5 was converted to the naturally occurring hydrocarbon ionene (6)



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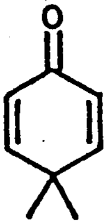

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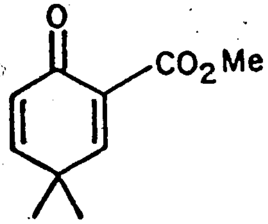

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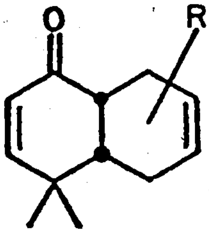

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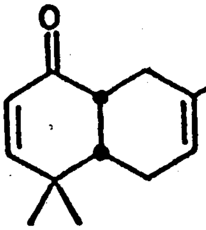

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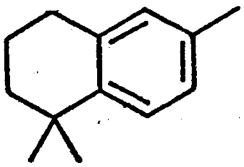

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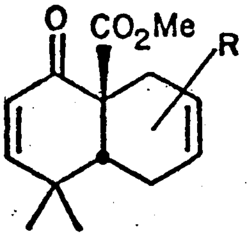
by Birch reduction and aromatization followed by Wolff-Kishner reduction. The dienone-ester 3 was found to add rapidly to a variety of hydrocarbon dienes under boron trifluoride etherate catalysis to give adducts of general formula 7. These adducts were formed in accordance with the normal rules of Diels-Alder addition with one exception. Addition of isoprene gave predominantly adduct 8. Examination of a series of Lewis acids as catalysts for reaction of isoprene with 3 showed that use of stannic chloride gave predominantly adduct 9. The same study showed that the use of ferric chloride



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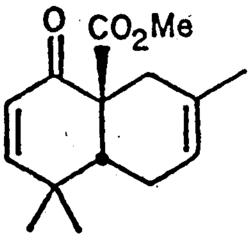

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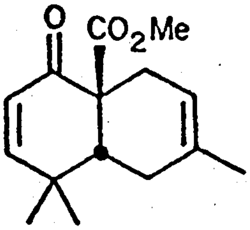

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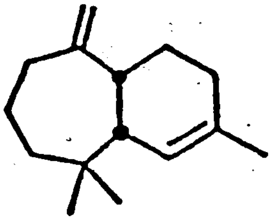
produced an unusually large increase (>100 times) in the rate of this Diels-Alder reaction relative to either boron trifluoride etherate or stannic chloride. The unusual formation of *anti-para* addition products 5 and 8 was attributed to a steric destabilization of the transition state leading to the normal *para*-addition product.

The synthesis of α-himachalene (10) and β-himachalene (11) has been achieved via adduct 9. A 1,4-reduction of the enone of 9 and decarbomethoxylation gave *trans*-ketone 12. Ring expansion of 12 with ethyl diazoacetate and decarbethoxylation of the resulting



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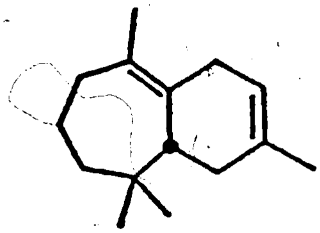

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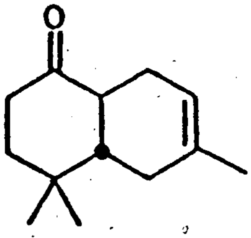

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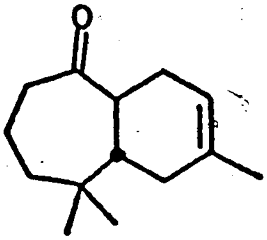
β-keto ester gave ketone 13 which was isomerized with acid to give ketone 14. Addition of methyllithium to 14 and dehydration of the resulting alcohol 15 gave α-himachalene (10) and β-himachalene (11).



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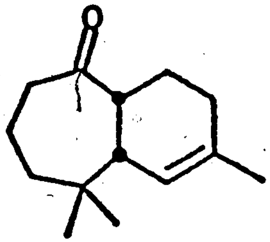

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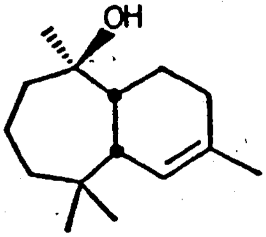

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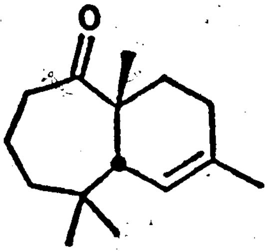
The syntheses of two reported naturally occurring ketones, isohimachalone (16) and *trans*-ketone 17 have also been approached via adduct 9. A 1,4-reduction of 9 and ketalization of the resulting ketone gave ketal 18. Reduction of the ester group of 18, formation



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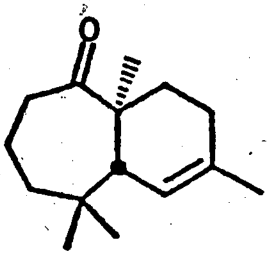

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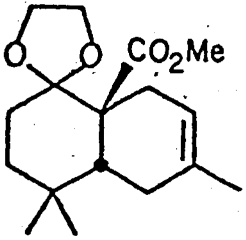

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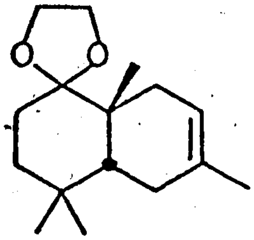
of the tetramethylphosphorodiamidate derivative of the resulting alcohol and dissolving metal reduction of the derivative gave the angular methyl substituted ketal 19. Cleavage of the ketal and migration of the double bond gave ketone 20. Ring expansion of 20 with ethyl diazoacetate and decarbethoxylation of the resulting β-keto ester gave *cis*-ketone 16 the spectral data of which were different from those reported for the naturally occurring ketone isohimachalone. The synthesis of *trans*-ketone 17 has been studied via ketone 20. Ketalization of 20 and allylic oxidation gave aldehyde 21 which was epimerized with base to give *trans*-aldehyde 22. Methods are under study for the conversion of 22 to *trans*-ketone 17.



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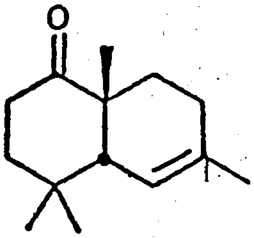

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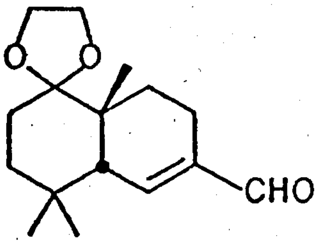

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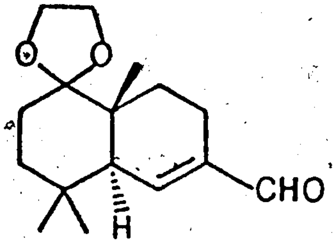

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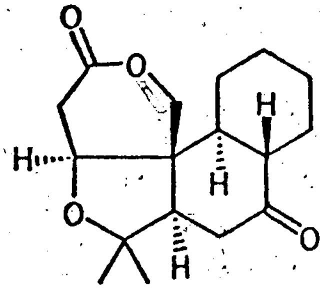
The construction of a model compound 23 possessing the AA'BC ring system of limonin 24 has been approached via Diels-Alder adduct 25. Epoxidation of the isolated double bond of 25 and acid catalysed rearrangement of the epoxide gave ketone 26. Thioketalization of 26 followed by 1,2-reduction of the enone and acetylation of the resulting alcohol gave acetate 27. Methods are under study for the further conversion of 27 to the model compound 23.



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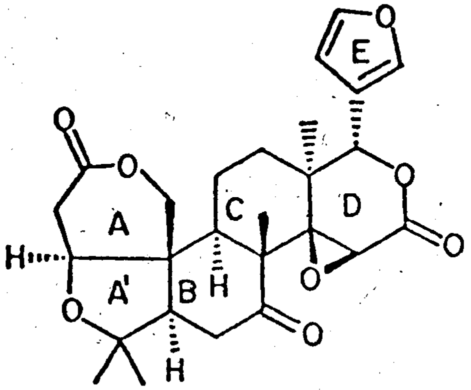

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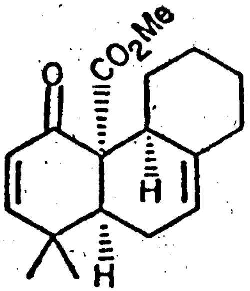

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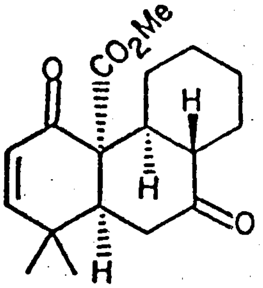

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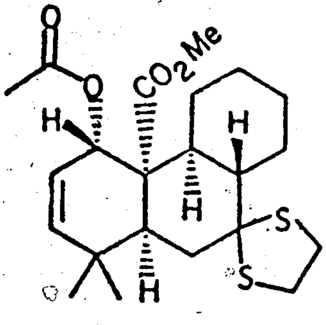

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CHAPTER 1

Diels-Alder Reactions of 4,4-Dimethyl-2-cyclohexen-1-ones

Introduction*

Since the cycloaddition of dienes with olefins (dienophiles) to give cyclohexenes was correctly formulated and seen to be a general process by Diels and Alder[13] few single reactions have achieved the same importance to the organic chemist. And yet at the same time few reactions have remained so long with the detailed nature of their mechanisms in question[5,14]. The modern formulation of the reaction as a concerted electrocyclic process[15] has recently received support from Frontier orbital calculations[14,16,17], which successfully predict the regioselectivity of the reaction. On the other hand, MINDO/3 calculations[18] indicate a highly unsymmetrical transition state in which the two new σ bonds are formed at two different "stages" of the reaction. The early development of a series of empirical rules predicting the structural outcome of the reaction has facilitated its use in organic synthesis. For example, the reaction has been used in classical syntheses of natural products such as cantharidin[19], cholesterol[20], cortisone[21], estrone[22] and reserpine[23].

The *cis*-principle predicts that addition to the diene in the required cisoid conformation occurs from the same side at each end of the diene moiety and also that attack at both ends of the dienophilic

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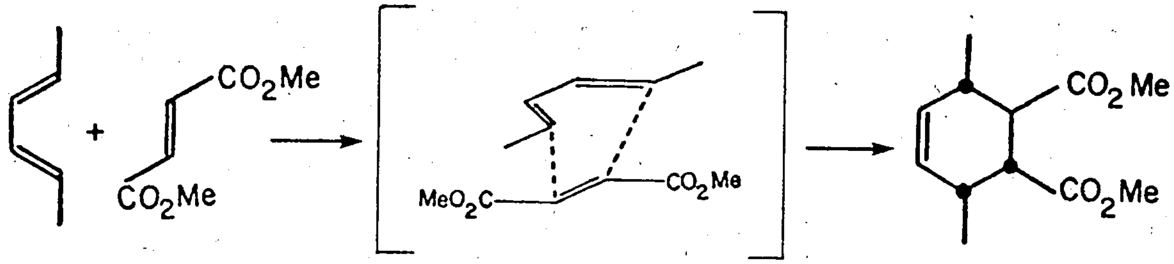
*For general references on the Diels-Alder reaction see references 1-12.

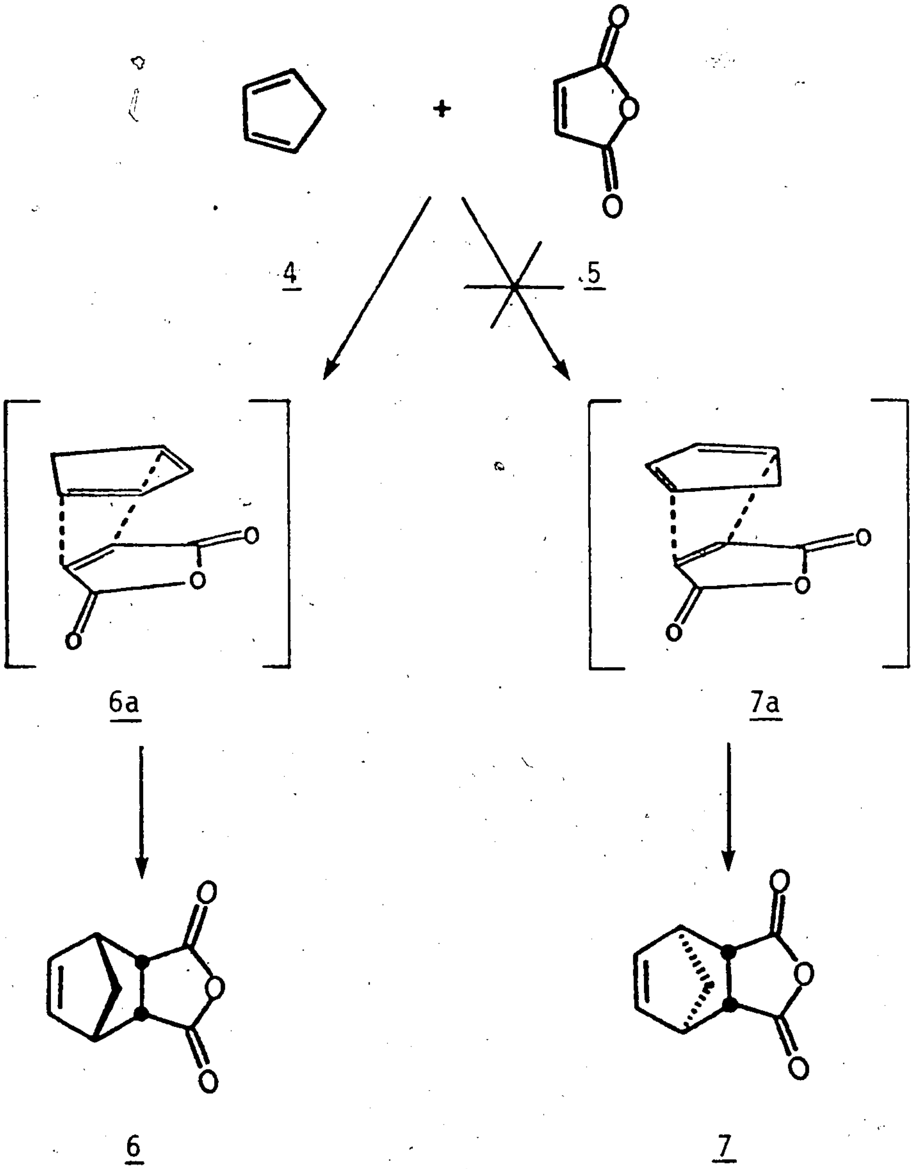
double bond occurs from the same face of the dienophile. It further predicts that the relative configurations of the substituents in the transition state (for example 3a) are preserved in the products. Thus *trans,trans*-2,4-hexadiene (1) reacts with dimethyl furmarate (2) to give adduct 3. The *cis*-principle is expressed in the modern formulation



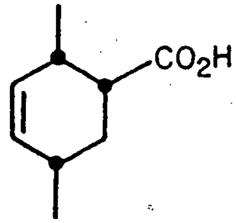
1 2 3a 3

of the reaction by Woodward and Hoffmann[15] as a concerted $2\pi s + 4\pi s$ cycloaddition reaction.

The *endo*-rule was originally formulated for additions of cyclic dienes and dienophiles to predict that, of the two possible "sandwich-like" transition states (for example 6a and 7a) the more favoured would be that with the "maximum concentration of double bonds"[3,5]. Thus reaction of cyclopentadiene (4) with maleic anhydride (5) proceeds to give only *endo*-adduct 6 and not *exo*-adduct 7[24]. The effect has been explained[15] by a stabilization of the transition state in which secondary orbital overlap[15] can occur between the π system of the diene and a π system in conjugation with the dienophilic double bond. Using this requirement it is evident that even in acyclic cases the term



"*endo*" is correctly used when the addition proceeds by a transition state in which secondary orbital overlap occurs, while "*exo*" refers to additions via transition states in which no secondary orbital overlap occurs. Thus according to the *endo*-rule *trans*, *trans*-2,4-hexadiene reacts with acrylic acid to give the *endo*-addition product 8 rather than the *exo*-addition product 9[25].



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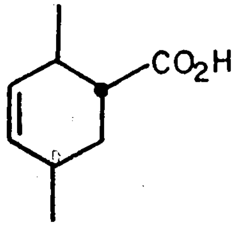

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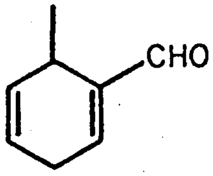
A group of orientational rules which predict the regiochemistry of additions between unsymmetrical dienes and dienophiles has also been developed. It has been shown that a substituent at C-1 of the diene promotes addition to give an adduct in which the substituent from the diene component is adjacent (*ortho*) to the substituent from the dienophile. In accordance with this *ortho*-rule, the principal product of addition of *trans*-piperlyne to propynal is adduct 10 rather than aldehyde 11[26]. In the case of 2-substituted dienes the substituent promotes form-



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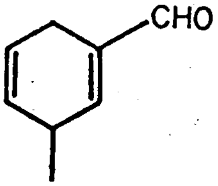

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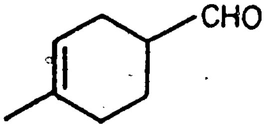
ation of the product having the two substituents in a *para*-relationship. Thus in accordance with the *para*-rule, addition of isoprene to acrolein gives predominantly aldehyde 12 rather than 13[27].



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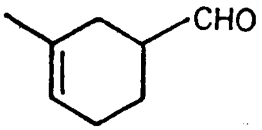

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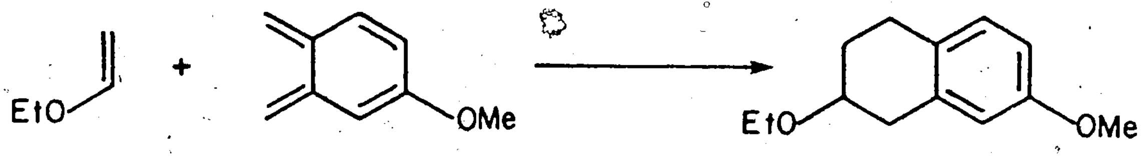
In the course of a study[16,17] of the regioselectivity of the Diels-Alder reaction using frontier orbital theory Houk predicted[16] that, where substituents of both diene and dienophile are electron donating, the favoured product should be that with the *meta*-orientation of the substituents.* This "*meta*-rule" has since been observed experimentally by Fleming[28]. Thus the major product of addition of ethyl vinyl ether (14) to diene 15 was adduct 16[28].



14 15 16

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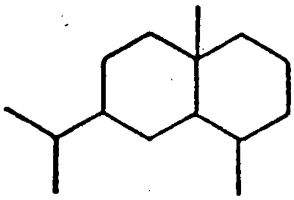
* This is also predicted by the heterolytic mechanism which, however, incorrectly predicts the same outcome when both substituents are electron withdrawing.[2]

In theory the application of the Diels-Alder reaction to the synthesis of *cis*-1-octatones requires only a straightforward addition of a cyclohexenone to an appropriately substituted diene. The method has the potential for rapid assembly of the decalin skeleton of a number of natural products such as those of the eudesmane (17), drimane (18) and cadinane (19) classes. As well, the unique stereo- and regioselectivity of the reaction promises that the required adducts could be obtained efficiently. Unfortunately, the thermal cycloaddition of dienes to cyclohexenone and its substituted analogs is notoriously recalcitrant. Cyclohexenones are much less reactive than cyclopentenones and early reports of low yields, and drastic conditions for the addition to cyclohexenones appear to have discouraged continued investigation on the direct generation of their adducts. For example, reaction of butadiene with cyclohexenone at 180-190° for 3 days reportedly gives adduct 20 in only 11% yield[29].



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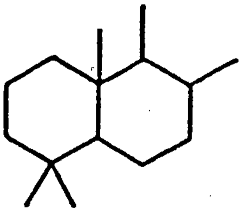

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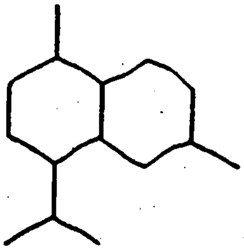

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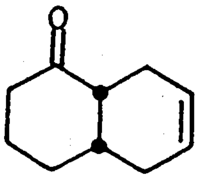
The observation that Lewis acid catalysis produces very large



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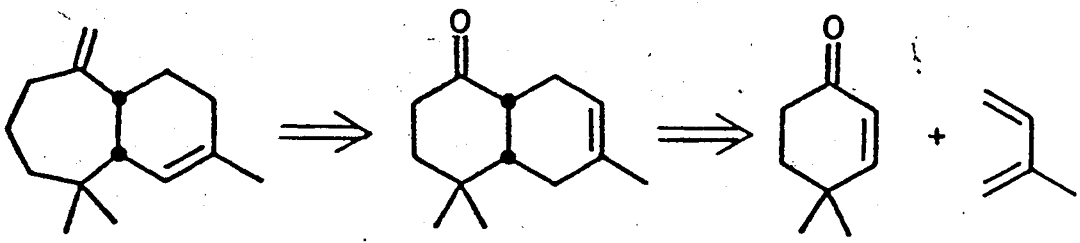
increases in the rates of the Diels-Alder additions of α,β-unsaturated carbonyl compounds[30,31,32] has made available many adducts which had previously been obtained only with difficulty (sealed tubes, high temperatures, etc.). Furthermore, it has been observed that such catalysis also has a marked effect on the regio- and stereoselectivity of the reaction so that the *ortho*-[33] and *para*-selectivity[34,35] of the addition as well as the *endo*-selectivity[36] are markedly increased. The application of Lewis acid catalysis to acyclic α,β-unsaturated carbonyl containing dienophiles has received fairly rapid recognition. However the delay of almost twenty years in application of these catalysts to simple cyclic conjugated enones is unexplained.

Recent investigations[37,38] have shown that the practice is equally applicable to cyclic enones. Kitahara[38] reports the aluminum chloride catalyzed addition of several dienes to 2-methyl-2-cyclohexen-1-one, and Wenkert[37] reports the aluminum chloride catalysed addition of butadiene to a series of cycloalkenones and 2-methylcycloalkenones. In both cases adducts are obtained in synthetically useful yields.

Our interest in Diels-Alder reactions of cyclohexenones arose from a proposal to synthesize the naturally occurring sesquiterpene α-himachalene (21) using the adduct 22 of 4,4-dimethyl-cyclohexenone (23) and isoprene as a key intermediate as outlined in the retrosynthetic scheme shown below. It was thought that under Lewis acid catalysis Diels-Alder addition to 23 might be possible. With this objective we proceeded with a study of the dienophilicity of enone 23 and several derivatives, with particular interest initially in the efficient generation of compounds of type 22 and later in the synthetic utility and structural aspects of the various adducts obtained.

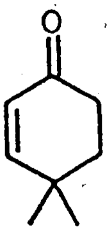


21 22 23

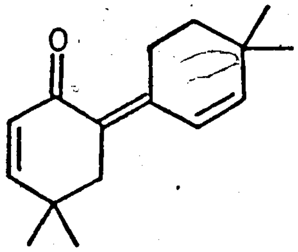
Results and Discussion

1. Diels-Alder Reactions of 4,4-Dimethyl-2-cyclohexene-1-one

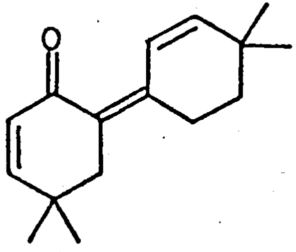
Enone 23 was easily prepared from isobutyraldehyde and methyl vinyl ketone according to the established procedure[39]. The direct Diels-Alder addition of isoprene to enone 23 was studied under a variety of conditions. The results are summarized in Table I. In general, Lewis acid catalyzed reactions in benzene, a common solvent for thermally promoted cycloadditions, produced only a mixture of products 24 and 25 (Entries 1-3). Compounds 24 and 25 could arise via Lewis acid induced enolization of 23 followed by condensation with another molecule of the enone. With a large excess of diene in a dilute solution of 23 at elevated temperature cycloaddition appeared to compete with condensation (Entry 4). An inseparable mixture was obtained (7% yield) of condensation products 24 and 25 together with a compound which showed nmr signals which could be attributed to either



23

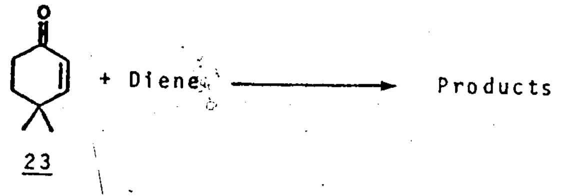


24



25

TABLE I. Additions to Enone 23



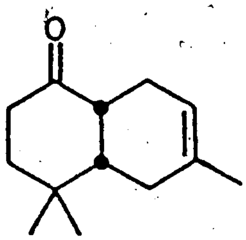
Entry	Catalyst (equiv.)	Solvent	Temp.	Time (days)	Diene (equiv.)	Products[a]
1	$BF_3 \cdot Et_2O$ (0.5)	benzene	25°	3	isoprene (4)	24 & 25
2	$BF_3 \cdot Et_2O$ (0.5)	benzene	80°	2	isoprene (4)	24 & 25
3	$AlCl_3$ (0.5)	benzene	80°	1	isoprene (4)	24 & 25
4	$BF_3 \cdot Et_2O$ (0.2)	benzene	80°	2	isoprene (20)	24, 25 & 22 or 26
5	$BF_3 \cdot Et_2O$ (0.1)	toluene	110°	2	isoprene (40)	22 or 26
6	$BF_3 \cdot Et_2O$ (0.5)	ether	25°	35	isoprene (20)	27
7	$BF_3 \cdot Et_2O$ (0.5)	ether	25°	3	butadiene[b]	--
8	--	mesitylene	250°[c]	4	isoprene (10)	complex mixture

[a] other than recovered 23

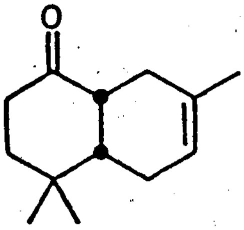
[b] excess gas bubbled into solution

[c] sealed tube

ketone 22 or 26*. The use of toluene as a solvent under similar conditions produced an impure sample (<14% yield) of 22 and/or 26 which was contaminated with polymeric material, but which did not contain any detectable trace of aldol-condensation products 24 and 25 (Entry 5).



22

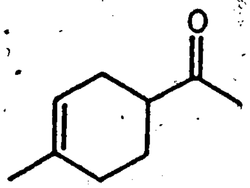


26

The use of ether as a solvent was found to entirely eliminate the self-condensation of 23 but unfortunately cycloaddition to 23 did not occur either (Entry 6). The only identifiable product of this reaction was ketone 27 (<10% yield) which could arise via moisture induced decomposition of 23. A 1,4-addition of water to enone 23 followed by a reverse-aldol condensation and a reverse-Michael addition could liberate methyl vinyl ketone which would be expected to add to isoprene under the reaction conditions to give 27.

---

*This identification was later confirmed by comparison with the nmr spectra of pure ketones 26 (*vide infra*) and 22 (see Chapter 2 of this thesis) however the product could not be obtained in sufficient purity to determine whether the material was 22 or 26 or a mixture of the two. It should be noted that the chemical shifts of the sharp signals in the spectra of authentic 22 and 26 are very similar and distinction of the two compounds was not feasible on impure samples.



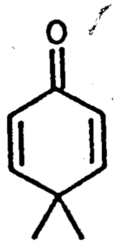
27

Addition of butadiene to 23 in ether at room temperature (Entry 7) gave only recovered starting material. Under thermal conditions (Entry 8) addition of isoprene gave a complex mixture of products as determined by gc analysis and it was not possible to determine with certainty whether ketones 22 and/or 26 were present.

These results show that 23 is a rather poor dienophile. Although it may yet be possible to achieve cycloaddition to 23 in synthetically useful yield by careful adjustment of the reaction parameters, it was more convenient for our purposes to investigate addition of dienes to a modified dienophile system.

2. Diels-Alder Reactions of 4,4-Dimethyl-2,5-cyclohexadiene-1-one.

Effective addition of the enone 23 to dienes appears to require both increased dienophilicity and protection of the molecule against side reactions such as aldol self-condensation. The introduction of a second double bond into the ring of enone 23 offers the dual advantage of preventing the troublesome aldol condensation experienced with 23 as well as enhancing the potential dienophilicity of the molecule both by increasing the number of dienophilic double bonds and by increasing the flatness of the molecule. With this in mind we examined the Diels-Alder reactivity of dienone <u>28</u> which was accessible by oxidation of enone <u>23</u> with selenium dioxide[40] or with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone[41].



<u>28</u>

It was found that in ether solution* with boron trifluoride etherate as the catalyst and using a large excess of diene, adducts were obtained in good yield over rather extended reaction times. The results of this study are summarized in Table II. In each case the *cis*-stereochemistry of the ring junction of the adduct was demonstrated by conversion with sodium hydroxide in aqueous methanol to the thermodynamically more stable *trans*-isomer as summarized in Table III. The regiochemistry of the Diels-Alder additions of unsymmetrical dienes were conclusively demonstrated by conversion of the pure *cis*- or *trans*-enones (or a mixture of the two) to aryl-ketone derivatives by treatment with *N*-bromosuccinimide[42,43] in refluxing carbon tetrachloride as

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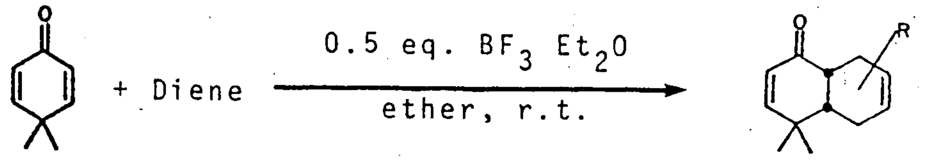
*Ether was found to be superior to benzene in this system since it gave higher yields of products and much less polymerization of the diene.

TABLE II. Diels-Alder Additions to Dienone 28



28

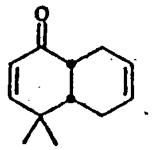
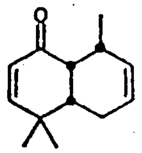
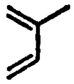
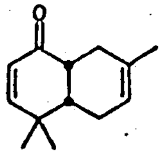
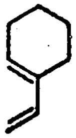
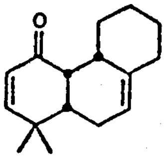
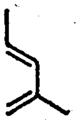
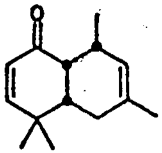
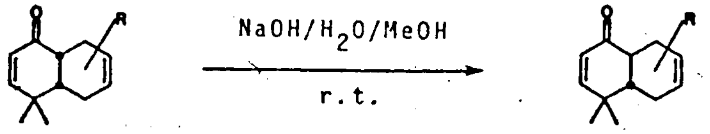
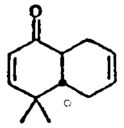
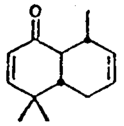
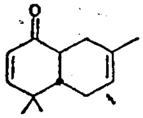
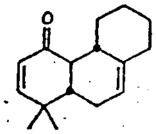
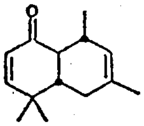
Entry	Diene (equiv.)	Time (days)	Yield	Adduct
9	 (excess)	22	26%	 29
10	 (30)	8	69%	 30
11	 (31)	22	61%	 31
12	 (4)	5	67%	 32
13	 (10)	7	20%	 33

TABLE III. Epimerization of Diels-Alder Adducts of 28



Entry	Adduct	Time (hr.)	Yield	cis/trans	Product
9[a]	29	26	72%	33:67	 34
10	30	20	64%	0:100	 35
11	31	1	87%	30:70	 36
12	32	24	49%	0:100	 37
13	33	20	44%	0:100	 38

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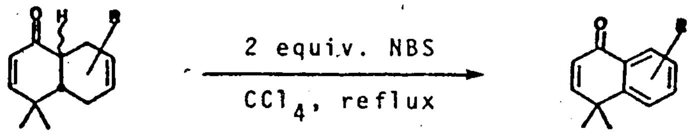
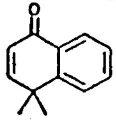
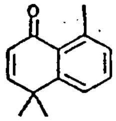
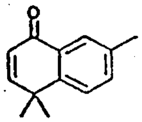
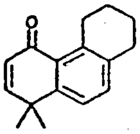
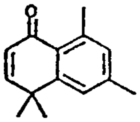
[a] The same entry number as in Table II is used for clarity since the results in both tables are grouped together in the discussion.

TABLE IV. Aryl-ketone Derivatives of Adducts of 28



Entry	Enone	Time (min.)	Yield	Product
9[a]	29 & 34 (33:67)	--	11%[b]	 39
10	30	30	12%	 40
11	31 & 36 (50:50)	45	38%	 41
12	32	60	30%	 42
13	33	60	17%	 43

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[a] See footnote a, Table III.

[b] The known ketone 39 was obtained by treating enones 29 and 34 with sodium amide in refluxing dimethylformamide for 24 hr.

summarized in Table IV. The structures of the resulting naphthalenones were unambiguously established by their nmr spectra.

A. Addition to Butadiene (Entry 9)

When an ether solution of dienone <u>28</u> and boron trifluoride etherate was kept saturated with butadiene by bubbling the gas into the solution for 15 min. and daily for 22 days* a single adduct was obtained in 26% yield based on consumption of 69% of the starting dienone <u>28</u>. The mass spectrum showed a molecular ion at m/e 176.1202 corresponding to a molecular formula of $C_{12}H_{16}O$ and the ir spectrum showed an absorption at 1675 cm^{-1} indicating the presence of an α,β-unsaturated ketone. The nmr spectrum displayed two vinyl protons as a multiplet at δ5.50, two enone protons as doublets (J = 10 Hz) at δ 5.72 and 6.31, and a *gem*-dimethyl group as singlets at δ1.31 and 1.10. These data indicated that a 1:1 adduct had been formed. If the adduct was formed in accordance with the *cis*-principle, then structure <u>29</u> could readily be assigned to the adduct.

In proof of its stereochemistry the adduct was subjected to epimerization. Treatment with sodium hydroxide in aqueous methanol for 20 hr. produced an equilibrium mixture of starting material and a new compound which were inseparable by column chromatography. The mass spectrum of the mixture showed a molecular ion at m/e 176.1222

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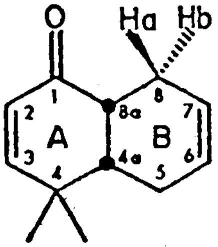
*A more satisfactory method of introducing butadiene to a reaction at atmospheric pressure and room temperature is to introduce a saturated solution of butadiene in benzene (~20% v/v in butadiene) to the ethereal solution of the dienophile[45].

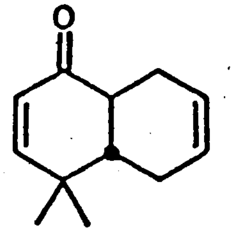


29

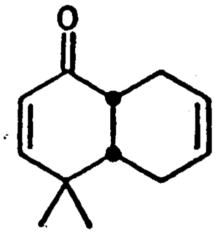
($C_{12}H_{16}O$) and the ir spectrum showed an enone absorption at 1680 cm^{-1}. The nmr spectrum of the mixture showed two sets of signals in an integral ratio of 67:33. The minor set of signals was identical with the spectrum of pure Diels-Alder adduct while the major set showed two enone protons as doublets (J = 10 Hz) at δ6.58 and 5.82, two vinylic protons as a multiplet at δ5.62 and methyl singlets at δ1.13 and 1.04.

Since in decalin systems the *trans*-fused isomer is expected to be more stable than the *cis*-fused isomer and to predominate under equilibrating conditions, it was apparent that the new compound was the *trans*-enone 34. Thus the Diels-Alder adduct must have the *cis*-ring junction defined by the structure 29. An examination of Table VI (see page 23) shows that the chemical shifts of several protons on enones of this series, particularly those of the C-3 and C-8a protons and the *gem*-dimethyl group, are significantly different in the *cis*- and *trans*-enones and these nmr signals were used routinely in assigning the stereochemistry of the substituted enones obtained in this work.

A detailed discussion of the nmr spectrum of 29 is warranted at

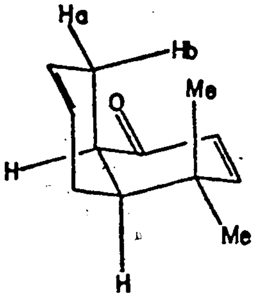


34

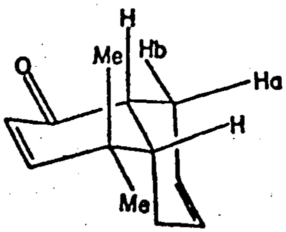


29

this stage in order to introduce several features which will be applied to other adducts in this series. Further examination of the nmr spectrum of 29 showed that the two protons at C-8 had quite different chemical shifts. The assignment of the doublet of multiplets at δ2.83 to Hb and the doublet of multiplets at δ1.94 to Ha was made after an examination of Dreiding models of the molecule. Of the two possible conformations for the molecule, 29a was expected to be of minor importance because of strong 1,3-diaxial interaction between the quasi-axial methyl group and the quasi-axial C-8 methylene group. In conformation 29b however this diaxial interaction is absent and 29b was proposed as the principal conformation of the molecule. In



29a



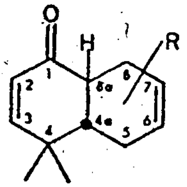
29b

this conformation the proton Hb is held in the deshielding zone of the carbonyl group and thus the signal appears at considerably lower field (δ2.83) than a normal allylic proton (δ2.0)[46]. Proton Ha is out of the plane of the carbonyl and further from it than Hb and so experiences virtually no deshielding by the carbonyl. This assignment was demonstrated conclusively using proton decoupling experiments on adduct 31 (*vide infra*) and was found useful in the assignment of stereochemistry at C-8 in adducts such as 35 and 38.

B. Addition to *trans*-Piperylene (Entry 10)[43]

The addition of *trans*-piperlene to dienone 28 under boron trifluoride etherate catalysis proceeded smoothly and relatively rapidly (complete reaction in 8 days) to give an adduct in 69% yield. The presence of 13 signals in the cmr spectrum (Table V) confirmed that the adduct was a single compound. The mass spectrum showed a molecular ion peak at m/e 190.1359 corresponding to the molecular formula $C_{13}H_{18}O$. The ir spectrum showed an absorption at 1686 cm^{-1} characteristic of an α,β-unsaturated ketone and a band at 716 cm^{-1} suggesting a *cis*-disubstituted double bond. The nmr spectrum (Table VI) indicated the presence of two coupled enone protons (J = 10 Hz) with signals at δ6.15 and 5.58. Two other vinyl protons appeared as multiplets at δ5.51 and 5.37 while methyl groups gave singlets at δ1.33 and 1.10 and a doublet (J = 8Hz) at δ1.38. The spectral data indicated that a 1:1 adduct had been formed and on the basis of the *cis*-principle, *ortho*-rule and *endo*-rule, structure 30 could tentatively be assigned to the adduct.

TABLE V. CMR Spectra (δ) of Some 4,4-Dimethyl-1-decalones

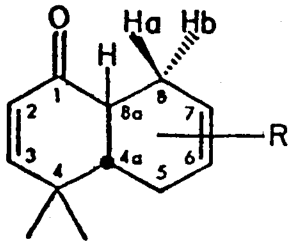


	cis-fused enones				*trans*-fused enones			
Carbon	30	31	32	33	35	36	37	23
1	200.9	199.6	201.1	201.0	202.5	a	201.7	198.4
2	124.0[b]	126.4	127.2	127.1[b]	123.6[b]	126.3	126.5	126.8
3	153.4	155.7	152.9	153.4	160.5	160.7	159.5	159.3
4	37.0	36.5	36.7	36.9	35.9	36.0	35.7	32.7
4a	47.0	43.1	47.1[b]	47.5[c]	49.4	43.4	48.6	36.2
5	25.0	24.5	25.0	30.0	25.4	26.1	25.2	--
6	127.0[b]	119.5	117.4	131.0	126.4[b]	119.4	116.5	--
7	132.0	132.5	138.1	126.5[b]	132.9	132.7	140.5	--
8	34.2	28.8	40.7	34.3	31.4	27.8	38.4	--
8a	47.8	42.4	46.9[b]	47.1[c]	44.2	42.3	43.5	34.4
gem CH_3	26.7	26.9	26.7	26.8	28.1	26.1	28.2	27.7
	26.0	26.2	26.0	26.0	20.6	21.0	20.6	27.7
R	19.0	23.3	34.1 28.9 26.5 26.2	23.3 19.2	23.2	23.2	37.0 36.0 23.4 26.5	

[a] Signal not discernable

[b,c] Assignment uncertain

TABLE VI. NMR Spectra (δ) of Substituted 4,4-Dimethyl-4a,5,8,8a-tetrahydro-1(4H)-naphthalenones



cis-fused enones

	29	30	47	31	48	32	33	59
C-2 H	5.72	5.58	5.70	5.68	5.68	5.57	5.53	5.67
C-3 H^a	6.31^b	6.15^b	6.27^b	6.28^b	6.29^b	6.12	6.13^b	6.25^b
C-6,7 H	5.55	5.51/5.37	5.7-5.4	5.18	5.33	5.08	5.19	5.38
C-8 Ha	1.94	2.34	--	1.87	c	<2.5^b	2.24	--
C-8 Hb	2.83	--	3.06	2.64	c	--	--	2.97
C-8a H^a	2.92	2.86	2.55	2.89	2.82	2.86	2.77	2.46
C-8 CH_3	--	1.38	1.04	--	--	--	1.33	0.97
C-6,7 CH_3	--	--	--	1.66	1.58	--	1.57	1.56
gem CH_3^{a}	1.31	1.33	1.30	1.30	1.30	1.28	1.31	1.28
	1.10	1.10	1.12	1.09	1.10	1.04	1.09	1.11

trans-fused enones

	34	35	63	36	78	37	38	79
C-2H	5.82	5.72	5.77	5.69	5.72	5.68	5.60	5.73
C-3H^a	6.58	6.49	6.60	6.55	6.56	6.45	6.45	6.57

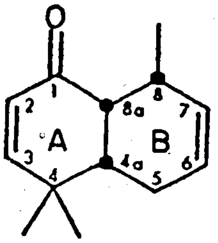
TABLE VI. (cont'd.)

	34	35	63	36	78	37	38	79
C-6,7 H	5.62	5.58/5.41	5.7-5.4	5.31	5.33	5.28	5.13	5.23
C-8 Ha	c	2.44	--	c	c	c	2.38	--
C-8 Hb	c	--	2.83	c	c	--	--	2.77
C-8 CH_3	--	1.19	0.81	--	--	--	1.17	0.75
C-6,7 CH_3	--	--	--	1.67	1.66	--	1.66	1.64
gem CH_3[a]	1.13	1.14	1.17	1.13	1.14	1.10	1.14	1.16
	1.04	1.06	1.04	1.03	1.04	1.02	1.07	1.02

[a] The signals for these protons were particularly useful for distinguishing the *cis*- from the *trans*-enones.

[b] This signal showed a long range W-type coupling to the proton at C-4a.

[c] The signal for this proton(s) was not clearly defined in the spectrum.



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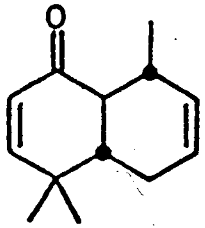
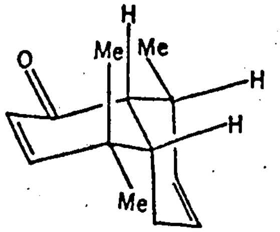
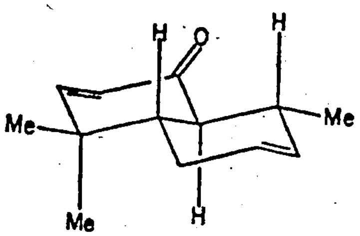


<u>35</u>

The *cis* ring-junction stereochemistry was indicated by the nmr spectrum. A long range W-type coupling of 1.5 Hz was observed in the signal at δ6.15 which was attributed to coupling of the proton at C-3 with the proton at C-4a. Examination of Dreiding models showed that a W-configuration of these two protons was possible only in the *cis*-enone <u>30</u> in which the proton at C-4a could assume a quasi-equatorial position relative to ring A in the preferred conformation <u>30a</u>. In the stable conformation (<u>35a</u>) of <u>35</u> the proton at C-4a is locked in



<u>30a</u>



<u>35a</u>

an axial position relative to both rings and cannot achieve a W-configuration with the proton at C-3. In proof of the ring junction stereochemistry, epimerization with sodium hydroxide in aqueous methanol, gave complete conversion to an isomeric enone in 64% yield[*].

The new enone showed a molecular ion at m/e 190.1360 ($C_{13}H_{18}O$) in the mass spectrum and the ir spectrum showed an enone band at 1677 cm^{-1} and an absorption at 694 cm^{-1} suggesting a *cis*-disubstituted double bond. The nmr spectrum showed two enone protons as doublets (J = 10 Hz) at δ6.49 and 5.72, and two other vinylic protons as doublets of multiplets (J = 12 Hz) at δ5.58 and 5.41. Methyl groups appeared at δ1.19 (doublet), 1.14 and 1.06 (singlets). On the basis of the relative stabilities of *cis*- and *trans*-decalones the new enone was assigned the *trans*-fused structure 35 and this assignment was supported by comparison of the nmr spectrum of 35 with that of *trans*-enone 34 (Table VI).

The *ortho*-orientation of the adduct was also indicated by the nmr spectrum. The proton at C-8a was a doublet of doublets indicating that it had only two adjacent hydrogens, as was the case in structure 30. The C-8a proton in the "*anti-ortho*"-adduct 45 was expected to show a

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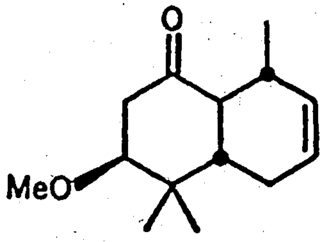
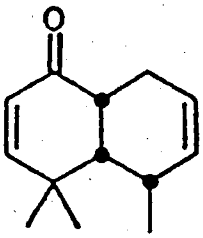
[*] The methoxy-ketone 44 was also obtained in 26% yield.



44

more complex signal as was observed for enone 29 where the proton in question was a broadened multiplet.



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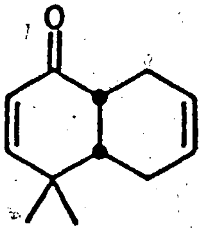

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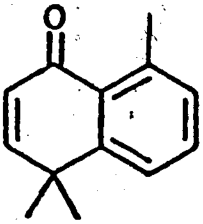
A more rigorous proof of the regiochemistry of this and similar adducts might be achieved by aromatization of the B ring. Such a derivatization of 30 would lead to aryl-ketone 40 whereas enone 45 would give aryl-ketone 46. Distinguishing these two aryl-ketones



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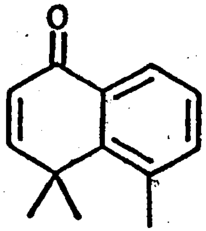
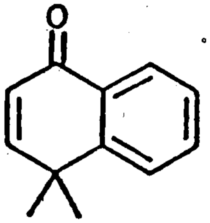


46

should be possible by inspection of their nmr spectra. The *peri*-effect[47] of the carbonyl on the proton or substituent at C-8, which is held in the deshielding zone of the carbonyl group, should cause the nmr signal of that proton or substituent to be shifted downfield significantly. For instance, the nmr spectrum of the known aryl-ketone 29[44] (in deuterochloroform) is reported to show a signal with a coupling



29

constant of 7 Hz at δ8.25 due to the *peri*-proton while the other aromatic protons show up as a multiplet between δ7.6 and 7.3. Thus the nmr of 40 would show a methyl singlet downfield from the normal benzylic methyl region of δ2.2[46] whereas 46 would show a one proton doublet downfield from the normal aromatic proton region of δ7.2[46].

The Diels-Alder adduct was aromatized with *N*-bromosuccinimide[42,43] in carbon tetrachloride at reflux for 30 min. The reaction gave a rather complex mixture of products from which an aromatic ketone could be isolated in 12% yield*. The mass spectrum of this compound showed a molecular ion at m/e 186.1039 corresponding to the molecular formula $C_{13}H_{14}O$. The ir spectrum had an absorption at 1663 cm^{-1} indicating an α,β-unsaturated ketone. The nmr spectrum showed an aryl methyl group as a singlet at δ2.70 and three aryl-protons at

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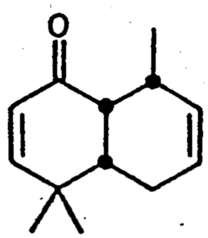
*The other products of this reaction were found to be brominated derivatives of 30 and 40.

δ7.30 (two protons) and 7.05. The absence of any signal above δ7.30 as well as the appearance of an aryl methyl group at low field were in agreement with the assignment of structure 40. Thus the regiochemistry of the Diels-Alder adduct must be as defined by structure 30.

It remained to determine the stereochemistry of the substituent at C-8. Normal *endo*-addition would give structure 30 whereas *exo*-addition would lead to enone 47. As mentioned in the discussion of



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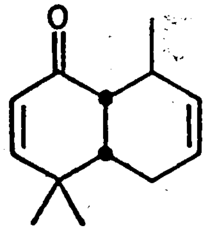

47

Entry 9, deshielding of the C-8 proton (or substituent) on the α-face of the molecule in its most preferred conformation should allow the distinction of these two enones on the basis of their nmr spectra. The allylic methine proton of 47 should be deshielded by the carbonyl and appear downfield from the normal value of δ2.6[46] while the methyl group at C-8 should be uneffected. On the other hand in 30 the methyl group should be shifted downfield from the normal value of δ1.0 and the allylic methine proton should be uneffected. Inspection of the nmr spectrum of the Diels-Alder adduct showed a methyl doublet at δ1.38 and a broad multiplet due to the allylic methine proton at δ2.34. These data were consistent with the assignment of structure 30 to the

Diels-Alder adduct.

The predicted effect of the carbonyl deshielding on the C-8 proton in enone 47 was confirmed by nmr analysis (Table VI) of an authentic sample of 47 prepared by another route (*vide infra*). The C-8 proton of 47 showed a signal at δ3.06.

C. Addition to Isoprene (Entry 11)[43]

In the presence of boron trifluoride, dienone 28 was found to add to isoprene smoothly but very slowly* to give a mixture of two products (61% yield) in a ratio of ~95:5 as determined by nmr and gc analysis. Except for the minor impurity the adduct was a single compound as determined by the presence of 13 major signals in the cmr spectrum (Table V). The mass spectrum showed a molecular ion at m/e 190.1354 corresponding to a molecular formula of $C_{13}H_{18}O$. The ir spectrum had a band at 1675 cm^{-1} due to an α,β-unsaturated ketone and a band at 827 cm^{-1} which suggested the presence of a trisubstituted double bond. The nmr spectrum showed two coupled enone protons (J = 10 Hz) at δ6.28 and 5.68 and one other vinylic proton as a broad singlet at δ5.18. The spectrum also indicated a *gem*-dimethyl group with singlets at δ1.09 and 1.30 and a vinylic methyl group as a singlet at δ1.66. The preceeding spectral data indicated that the product was a 1:1

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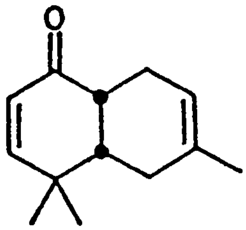
*The long reaction times (21-65 days) invariably resulted in production of a large amount of polymerized diene which was easily separated by column chromatography.

adduct of 28 with isoprene. Assuming that the addition occurred according to the *cis*-principle and the *para*-rule, structure 48 could be assigned.

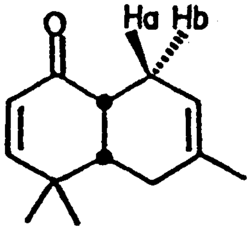


48

The *cis*-stereochemistry of the adduct was indicated after comparison of its nmr spectrum with those of *cis*-enones 29 and 30 (Table VI). To confirm the stereochemistry, the adduct was equilibrated with base. Treatment with sodium hydroxide in aqueous methanol rapidly gave an equilibrium mixture of the starting material and an isomeric enone in a ratio of 30:70 as determined by nmr integration and gc analysis.

The product enone was obtained pure by recrystalization from ether and gave a molecular ion at m/e 190.1359 in the mass spectrum indicating the chemical formula $C_{13}H_{18}O$ isomeric with the starting enone. The ir spectrum showed a band at 1673 cm^{-1} due to a conjugated enone and a band at 790 cm^{-1} suggesting a trisubstituted double bond. The nmr showed two coupled enone protons at δ6.55 and 5.69 and another vinylic proton as a multiplet at δ5.31. A vinylic methyl group appeared as a broadened singlet at δ1.67 and a *gem*-dimethyl group appeared as singlets at δ1.13 and 1.03. The generation of the new enone as the major component of the base equilibration defined the stereochemistry of the new component as *trans*[*] and that of the original adduct as *cis*.

The undecoupled proton nmr spectrum of the adduct did not offer any assurance of its regiochemistry. A proton nmr decoupling study however showed that irradiation of the vinyl proton at δ5.18 caused no change in the signal due to proton Ha at C-8 (δ2.64) but did cause a change in the signal due to the methylene protons at C-5 (δ1.95). Similarly irradiation of the proton Ha at C-8 (δ2.64) had no effect on the signal due to the vinyl proton (δ5.18) whereas irradiation of the C-5 methylene group (δ1.95) induced a distinct sharpening of the vinyl proton signal at δ5.18. These data were inconsistent with the assignment of structure 48 to the Diels-Alder adduct and were more easily reconciled with structure 31.



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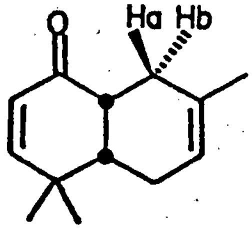

31

As discussed in the preceeding section an effective means of

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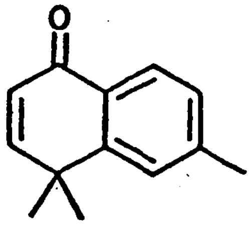
[*] The *trans*-isomer was identified by and gc analysis as the minor (~5%) component of the original Diels-Alder reaction product.

distinguishing 31 and 48 would be to aromatize the B ring. The resulting aryl-ketone--either 41 or 49--could be unambiguously



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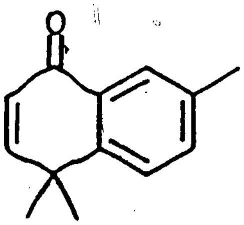

49

identified by its nmr spectrum since in 41 the low field *peri*-proton at C-8 should be a singlet whereas in 49 the corresponding proton should appear as a doublet with a coupling constant of ~9 Hz[46].

On reaction with selenium dioxide in refluxing *t*-butanol-acetic acid for 20 hr. the adduct gave an aryl-ketone in 13% yield. The mass spectrum of the product showed a molecular ion at m/e 186.1053 corresponding to the molecular formula $C_{13}H_{14}O$. The ir spectrum had a band at 1665 cm^{-1} indicating an α,β-unsaturated ketone. The nmr spectrum showed a signal due to the *peri*-proton at δ 7.90. The signal was sharp with a fine splitting of less than 1 Hz*. This was consistent only with assignment of structure 41 to the aryl-ketone derivative. Clearly then, the Diels-Alder adduct must have structure 31 and the *trans*-enone derived from it must have structure 36.

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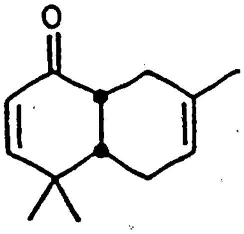
*The fine splitting was attributed to a 1,3-aromatic coupling.



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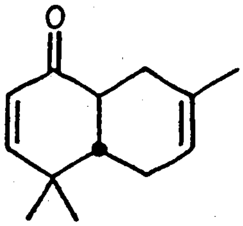
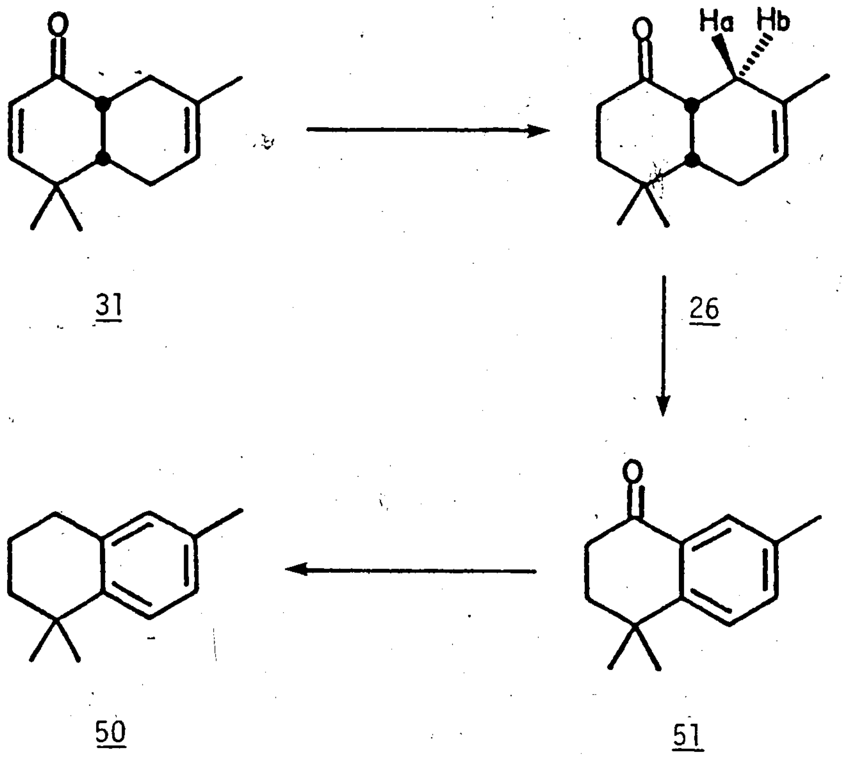


36

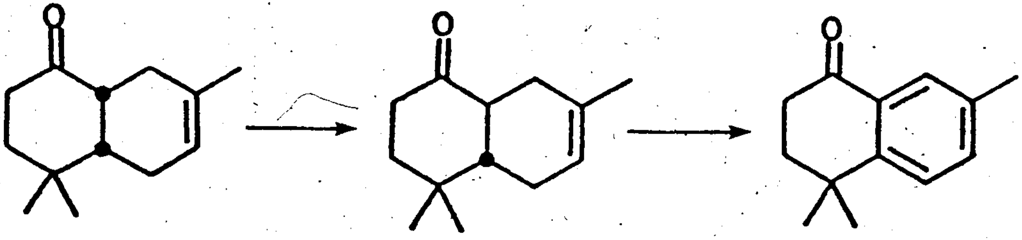
Since aryl-ketone derivatives such as 41 were useful for routine characterization of the adducts in this series a search was undertaken for a method of generating them in synthetically useful yields. The best result obtained was dehydrogenation with *N*-bromosuccinimide in refluxing carbon tetrachloride for 45 min. which was found to convert a 50:50 mixture of enones 31 and 36 to aryl-ketone 41 in 38% yield. These conditions also produced a number of by-products, mainly brominated derivatives of 31, 36, and 41.

As a further proof of its structure the Diels-Alder adduct 31 was converted[43] to ionene (50), a naturally occurring aromatic hydrocarbon found in wild carrot fruit[48] and peach foliage[49] as well as in cigarette smoke[50] where it arises from pyrolysis of β-carotene[50,51]. Birch reduction of 31 with lithium in ammonia[52] gave a single ketone 26 in 78% yield. The mass spectrum of 26 showed a molecular ion at m/e 192.1520 corresponding to the molecular formula $C_{13}H_{20}O$. The ir spectrum had an absorption at 1712 cm^{-1} indicating a saturated ketone and the nmr spectrum showed a vinyl proton as a multiplet at δ5.19, a vinylic methyl group as a broadened singlet at δ1.64 and a *gem*-dimethyl group as singlets at δ1.32 and 0.97.



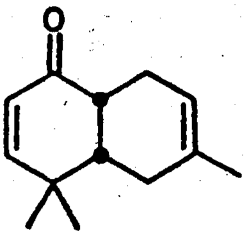
Treatment of ketone 26 with two equivalents of *N*-bromosuccinimide[42,43] in refluxing carbon tetrachloride gave a rather complex mixture of products from which aryl-ketone 51 could be isolated in 35% yield by careful column chromatography on silica gel. The mass spectrum of 51 showed a molecular ion at m/e 188.1195 corresponding to the molecular formula $C_{13}H_{16}O$. The ir spectrum showed an absorption due to an aryl-ketone at 1686 cm^{-1}. The nmr spectrum displayed a *gem*-dimethyl group as a singlet at δ1.34, an aryl methyl group as a singlet at δ2.32 and three aryl protons as singlets at δ7.18, 7.19 and 7.69 (*peri*-deshielded).

In a slightly more efficient synthesis of aryl-ketone 51, epimerization of *cis*-ketone 26 with sodium hydroxide in aqueous methanol gave a 14:86 mixture (91% yield) of 26 and the more stable *trans*-isomer 52. Separation by column chromatography gave pure *trans*-ketone 52 which was converted to aryl-ketone 51 with *N*-bromosuccinimide in 45% yield.



26 52 51

Aryl-ketone 51 was reduced by a modification of the Wolff-Kishner reaction[53] to give a hydrocarbon in 60% yield (12.2% in 5 steps from 28) which was identical in all respects (nmr, ir, ms, and cmr) with an authentic sample of ionene (50)[54] prepared from β-ionone (53). The identity of the synthetic material with authentic ionene (50) requires that the starting adduct have structure 31 and not structure 48.



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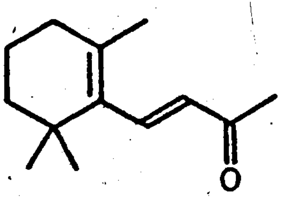
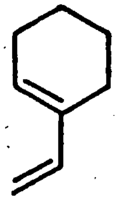


53

D. Addition to 1-Vinylcyclohexene (Entry 12)

In the presence of boron trifluoride etherate, 1-vinylcyclohexene (54)[55*] was found to add to dienone 28 to give a 1:1 adduct in 67% yield. The presence of 16 lines in the cmr spectrum (Table V) showed that the adduct was a single compound. The molecular ion at m/e 230.1666 in the mass spectrum corresponded to the chemical formula $C_{16}H_{22}O$. The ir spectrum showed a band due to an α,β-unsaturated ketone at 1686 cm^{-1}. In the nmr spectrum doublets (J = 10 Hz) at δ6.12 and 5.57 indicated two enone protons and a broad singlet at δ5.08 indicated another vinyl proton. A *gem*-dimethyl group appeared as singlets at δ1.28 and 1.04. For 1,2-disubstituted dienes such as 1-vinylcyclohexene (54), to which both *ortho*- and *para*-rules might apply, it has been found that the *ortho*-rule governs the course of the reaction[1]. If the adduct was also formed in accordance with the



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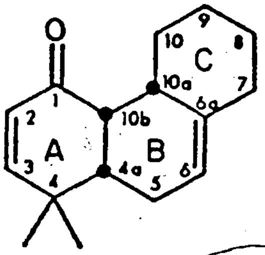
[*] For an efficient preparation of 1-vinylcyclohexene see Chapter 3 of this thesis.

ortho-rule, the expected structure of the adduct would be 32[*].



32

The *cis*-stereochemistry of the AB ring fusion was indicated after comparison of the nmr spectrum of the adduct with others in this series (Table VI). Conclusive proof was accomplished by base catalysed epimerization with sodium hydroxide in aqueous methanol to give the isomeric *trans*-enone in 49% yield[**] and no detectable trace of the starting adduct.

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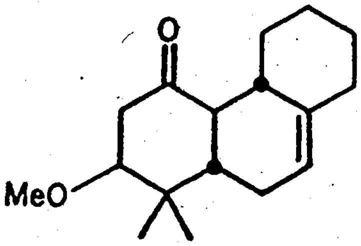
[*] The numbering scheme shown in structure 32 differs from that recommended by IUPAC and Chemical Abstracts but is used in this chapter to be consistent with other compounds in this series.

[**] The methoxy-ketone 55 was also obtained in 12% yield.



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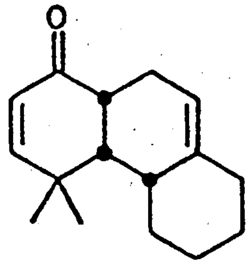
The mass spectrum of the *trans*-enone showed a molecular ion at m/e 230.1667 indicating the chemical formula $C_{16}H_{22}O$. The ir spectrum showed an α,β-unsaturated carbonyl absorption at 1673 cm^{-1} and a band at 799 cm^{-1} suggesting a trisubstituted double bond. The nmr spectrum showed two enone proton doublets at δ6.45 and 5.68 and a broad vinyl proton singlet at δ5.28 as well as methyl singlets at δ1.11 and 1.02. These nmr data correspond closely to those of other *trans*-enones in this series (Table VI).

The *ortho*-orientation of the adduct was indicated by the nmr spectrum. The signal at δ3.00 due to the methine proton adjacent to the carbonyl was a doublet of doublets with coupling constants of 3Hz each, similar to the spectrum of enone 30. If the adduct had the regiochemistry defined by structure 56 a more complex signal would be expected for that proton, as was observed for 29 and 31. In unambiguous proof of the regiochemistry, the *trans*-isomer (37) derived from the adduct was converted to the now familiar ring B aromatic derivative in 30% yield with *N*-bromosuccinimide, in refluxing carbon



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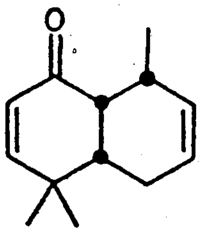

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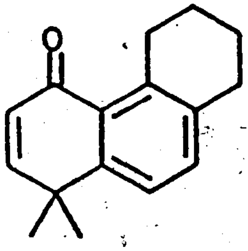
tetrachloride for 1 hr.[42,43] The nmr spectrum of the aryl-ketone showed two signals due to aromatic protons at δ7.17 and 7.13 and had no signals further downfield. Furthermore a signal attributable to a benzylic methylene group in the *peri*-position was found at δ3.24, downfield from the normal range of δ2.6[46]. Since the ketone 57 should show a deshielded *peri*-proton and no deshielding of its benzylic methylene groups these data confirmed the assignment of structure 42 to the aryl-ketone derivative and the regiochemistry of the adduct and its *trans*-isomer as defined by structures 32 and 37 respectively.



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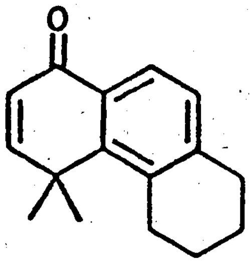

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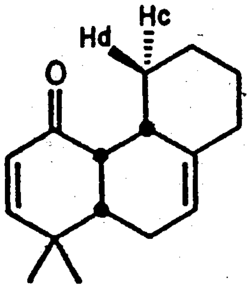

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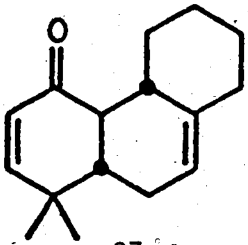
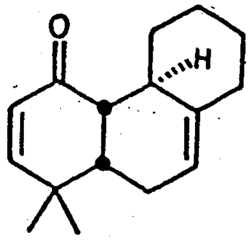


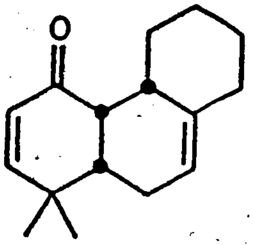
37

It remained to confirm the stereochemistry at C-10a of 32 and 37. The nmr signal due to the proton at C-10a could not be identified in the spectrum of 32. However the only two signals in the range where we might expect to find the signal due to the deshielded C-10a proton of 58 (*vide supra*, Entry 9) were easily attributed to other



58

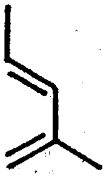
protons. One signal ($\delta 2.86$) was clearly the ring junction proton at C-10b. The other ($\delta 2.50$) was a doublet of doublets of doublets of doublets with three coupling constants of 12 Hz and one of 4 Hz. This signal was too complex to represent a proton at C-10a which has only three neighboring protons. A careful examination of Dreiding models showed that in structure 32 one of the protons on C-10 (Hc) lies in the deshielding zone of the carbonyl group and would be expected to be shifted downfield from its normal region[46] of $\delta 1.4$. This proton would experience two diaxial couplings, one geminal coupling, and one gauche coupling. This fit well with the observed couplings of the signal at $\delta 2.50$. No other proton in enone 32 would be expected to exhibit such a shift and coupling pattern nor would any proton in structure 58. The absence of any other signal in the region $\delta 2.5$ to $\delta 5.0$ would appear to rule out structure 58 as the identity of the adduct while the deshielded proton at C-10 indicated that the adduct must have the stereochemistry defined by structure 32.



32

E. Addition to *trans*-2-Methyl-1,3-pentadiene (Entry 13)

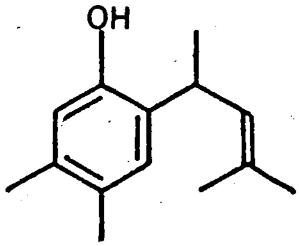
Dienone 28 reacted with *trans*-2-methyl-1,3-pentadiene (59) under boron trifluoride etherate catalysis to give two products in a total



59

yield of 57% (based on consumption of 88% of the starting dienone) and in a 50:50 ratio. The two products were separated by flash chromatography[56].

One product gave a molecular ion at m/e 204.1508 ($C_{14}H_{20}O$) in the mass spectrum and its ir spectrum had a band at 3438 cm^{-1} indicating a hydroxyl group. The nmr spectrum showed singlets due to two aromatic protons at δ6.73 and 6.38, and a vinyl proton as a doublet of multiplets at δ5.18. A hydroxyl proton appeared as a broad singlet at δ4.91 while five methyl groups were indicated by a six-proton singlet at δ2.14, (benzylic), two finely split doublets (J = 1 Hz) at δ1.70 and 1.66 (allylic) and a doublet (J = 7 Hz) at δ1.24. On the basis of these spectral data the structure of this product was assigned as phenol <u>60</u> which probably was formed via Lewis acid

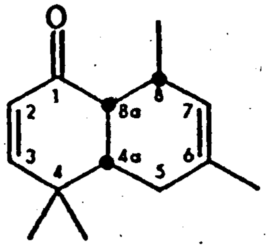


<u>60</u>

induced dienone-phenol rearrangement[57] of dienone <u>28</u> followed by Friedel-Crafts alkylation with diene <u>59</u>.

The other product showed a molecular ion at m/e 204.1510 corresponding to the molecular formula $C_{14}H_{20}O$. Its ir spectrum had bands at 1687 cm^{-1} and 815 cm^{-1} indicating an α,β-unsaturated ketone and a trisubstituted double bond respectively. The nmr spectrum showed two coupled enone protons (J = 10 Hz) at δ6.18 and 5.53 and a vinyl proton as a broad singlet at δ5.19. Methyl groups appeared as singlets at δ1.31, 1.09 (*gem*) and 1.57 (vinylic) and a doublet at δ1.33. The cmr spectrum (14 lines, Table V) confirmed that the enone was a single compound and its spectral data indicated that it was the product of Diels-Alder addition of diene 59 to dienone 28.

The Diels-Alder adduct, if formed according to the usual rules, would have structure 33. The *cis*-ring fusion was indicated by the nmr spectrum. The signal for the proton of C-3 showed a long range W-type coupling[47] of 2 Hz with the proton at C-4a and, as discussed in the case of enone 30 (Entry 10) such a relationship is only possible in the *cis*-isomer. In proof, the adduct was converted with sodium hydroxide in aqueous methanol to the isomeric *trans*-enone in 44% yield*.



33

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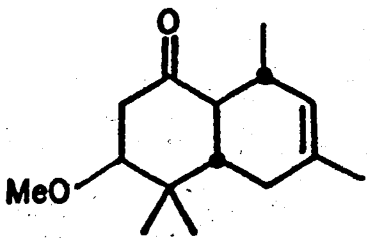
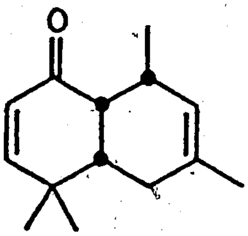
*The ketone 61 was also isolated in 24% yield.



61

The mass spectrum of the *trans*-enone showed a molecular ion at m/e 214.1505 ($C_{14}H_{20}O$) and the ir spectrum showed an enone absorption at 1673 cm^{-1}. The nmr spectrum showed two enone protons as doublets (J = 10 Hz) at δ6.45 and 5.60 and a vinyl proton as a broad singlet at δ5.13. Methyl groups appeared as singlets at δ1.66 (vinylic) 1.14 and 1.07 and a doublet at 1.17.

The regiochemistry of the adduct was also indicated by the nmr spectrum. The signal due to the proton at C-8a (δ2.77) was a distinct doublet of doublets with coupling constants of 4 Hz and 3 Hz indicating that proton had only two neighboring protons, as was the case in structure 33. The C-8a proton in 62 would show a more complex signal.



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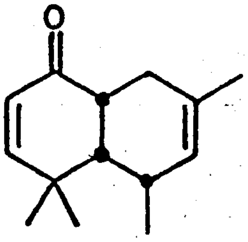
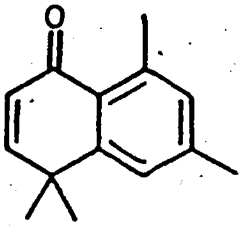


62

In proof the adduct was converted (17% yield) to the aryl-ketone derivative with *N*-bromosuccinimide in refluxing carbon tetrachloride. The nmr spectrum of the aryl-ketone showed two aromatic protons at δ7.06 and 6.86 and two aryl methyl singlets at δ2.64 and 2.34. The presence of the deshielded *peri*-methyl group (δ2.64) and the absence of a *peri*-proton indicated that the aryl-ketone has structure

43 and thus the regiochemistry of the adduct must be defined by structure 33.

The C-8 stereochemistry of the adduct could be deduced from the nmr spectrum in a manner analagous to that used in the discussion of enone 30 (Entry 10). The allylic methine proton at C-8 of 63 should be deshielded by the carbonyl group and appear downfield from the normal value of δ2.6[46] while the methyl substituent should be unaffected. Conversly the allylic methine of 33 should be unaffected and the C-8 methyl group should be deshielded relative to the normal value of δ1.0[46]. The adduct showed a methyl doublet at δ1.33 and a methine proton coupled to it at δ2.24. These data are consistent with structure 33 and not with 63*.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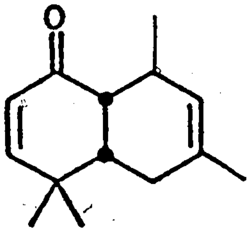
63

The preceeding results show that dienone 28 is a useable though moderately weak dienophile. Addition to simple hydrocarbon dienes

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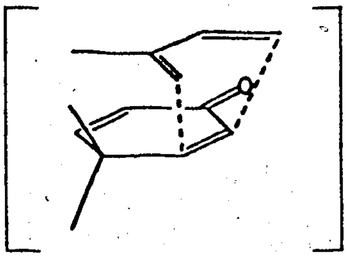
*The predicted effects of the carbonyl deshielding on substituents at C-8 in enone 63 were confirmed by nmr analysis of an authentic sample of 63 prepared by another route (*vide infra*).

proceeds smoothly if somewhat slowly to give generally acceptable yields of adducts. The most important item of note is the total violation of the *para*-rule in the case of addition to isoprene (Entry 11). The normal addition of 1-substituted dienes (Entries 10 and 12) leads to the conclusion that the cause of the abnormal addition of isoprene is a steric one in which the substituent at C-2 of the diene interacts with a substituent at C-4 of the dienophile as shown below[*]. If the steric effect were sufficiently strong the electronically favoured *para*-addition would be excluded and the less favourable *anti-para*[**] addition would predominate.



48a

Comparison of the various dienes is interesting in this context. *trans*-Piperylene (Entry 10) would not be expected to encounter any

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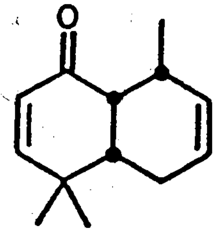
[*] A similar explanation has been offered to account for the relatively poor dienophilicity of cyclohexenones6.

[**] We have adopted42 the term "*anti-para*" to describe additions in violation of the *para*-rule. Ordinarily the regiochemistry of the adduct might be referred to as "*meta*" since the substituent on the diene is *meta* to the directing substituent--the carbonyl group--in the product. However we wish to make a clear distinction between addition in *violation* of the *para*-rule and addition in accordance with the *meta*-rule.

steric barrier to normal *ortho*-addition and the *ortho*-addition product 30 is the only one observed. Similarly, only the expected product 32 is obtained from 1-vinylcyclohexene (54) (Entry 12) since the *ortho*-rule takes precedence over the *para*-rule and at the same time the steric interaction between the diene and the methyl group of the dienophile acts to promote addition in the same direction as the electronic control.



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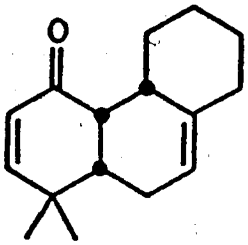
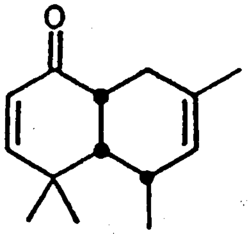


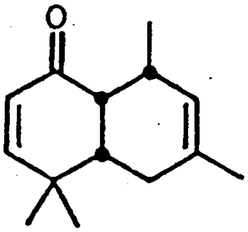
32

The addition of *trans*-2-methyl-1,3-pentadiene (55) however raises an important point since the steric effect acts in opposition to the combined directing influence of the *ortho* and *para* rules. This offers the opportunity to determine the strength of the steric effect relative to the combined electronic effects. Total steric control would produce only enone 62 whereas electronic control would result only in formation of 33. As we have seen, enone 33 is the only Diels-Alder addition product, indicating that a stronger electronic directing effect might be used to counteract the steric effect.

One possible method to increase the strength of the electronic



62



33

directing effect of 28 might be the use of a stronger, and therefore more electron-withdrawing Lewis acid as the catalyst. The larger induced polarization of the dienophilic double bond should act to promote *para*-addition. Unfortunately the use of boron tribromide (benzene, room temperature, 11 days) did not produce any detectable trace of adducts of 28 with isoprene. Two other catalysts were also examined. Stannic chloride (ether, room temperature, 11 days) gave no detectable trace of Diels-Alder adduct and ferric chloride (ether, room temperature, 7 days) produced an adduct in 3% yield which nmr analysis showed to be almost exclusively enone 31*.

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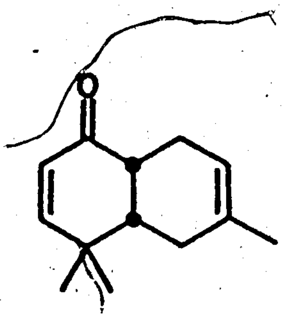
*This was confirmed by comparison (gc, nmr) with authentic enones 48 (*vide infra*) and 31 (*vide supra*).



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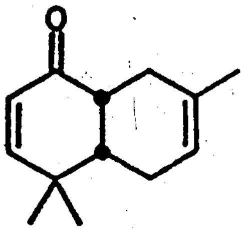

31

Although Diels-Alder additions to dienone 28 produce acceptable yields of useful adducts, the long reaction times might tend to discourage its general acceptance as a dienophile. Furthermore, in the case of *para*-rule directed additions, the total violation of the electronic directing effect renders such *para*-substituted adducts inaccessible. On the basis of the Alder rule* one method of increasing the reaction rate would be to place an additional electron withdrawing substituent on the dienophilic double bond. This would increase the polarization of that bond and thus increase the strength of the electronic *para*-directing effect on 2-substituted dienes as well as the reaction rate. With an appropriate choice of substituent it might prove possible to totally overcome the steric effect which promotes the observed *anti-para* addition.

3. Diels-Alder Reactions of 2-Carbomethoxy-4,4-dimethyl-2,5-cyclohexadien-1-one[58].

In an effort to test these assumptions the dienone-ester 64 was examined. The choice of a carbomethoxyl group as an activating substituent offers several features. It can be easily removed from the resulting β-keto-esters by decarboxylation and it offers a level of functionalization which might be used effectively in synthetic

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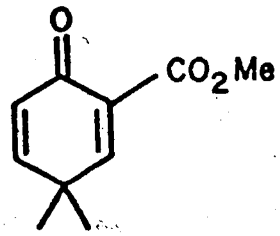
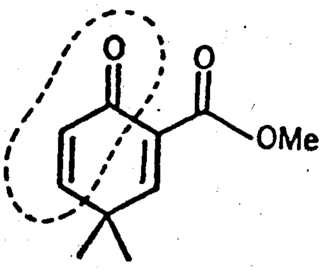
*The Alder rule predicts that substitution of an electron withdrawing substituent on the dienophilic double bond increases the reactivity of that bond and that substitution of electron donating substituents on the diene increases the reactivity of the diene[5].



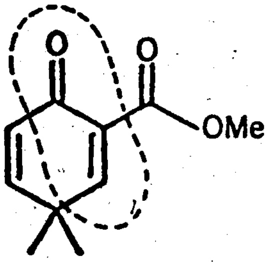
<u>64</u>

schemes (for example see Chapters 2 and 3 of this thesis).

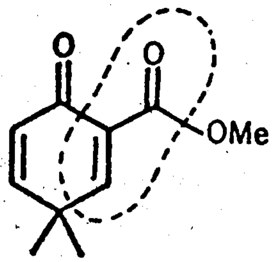
It can be seen that there are in fact three dienophilic moieties in the molecule as illustrated below. On the basis of the Alder rule the unsubstituted enone system of <u>64a</u> is expected to be relatively unreactive and addition to either <u>64b</u> or <u>64c</u> would occur. Ordinarily it would be unnecessary to distinguish these two moieties except in cases where the *endo*-rule comes into effect. *Endo*-addition to <u>64b</u> would give a product different from that of *endo*-addition to <u>64c</u>. The factor determining which system would dominate the reaction pathway is expected to be a function of which one would offer the most effective secondary orbital overlap with the diene. However in the case of addition of 2-substituted butadienes it is apparent that *endo*-addition



<u>64a</u>



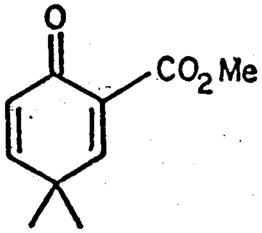
<u>64b</u>



<u>64c</u>

to 64c would totally eliminate the steric effect between the substituent and the methyl groups of the dienophile which might be experienced in *endo*-addition to 64b. This could contribute to the production of the electronically favoured product in the addition of 2-substituted dienes.

Dienone ester 64 was easily prepared from enone 23[58]. Carbomethyoxylation of 23 with sodium hydride and dimethyl carbonate in



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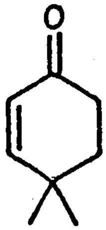

23

refluxing 1,2-dimethoxyethane[59] gave keto-ester 65 in 61% yield*. Dehydrogenation with 2,3-dichloro-4,5-dicyano-1,4-benzoquinone (DDQ)[41] produced only a trace of the desired product 64. However

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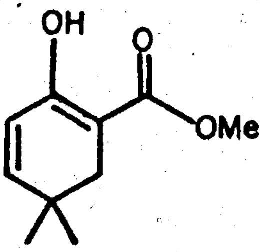
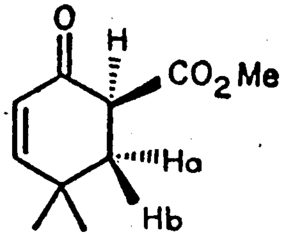
*The keto-ester 65 exists partially in the enol form 65a.



65a

treatment with selenium dioxide in refluxing *t*-butanol-acetic acid gave a product readily identifiable as dienone-ester 64 in 80% yield along with a small amount of the transesterification product 66



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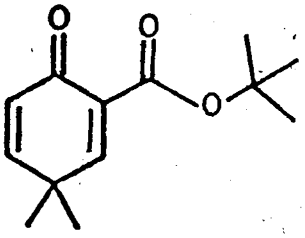


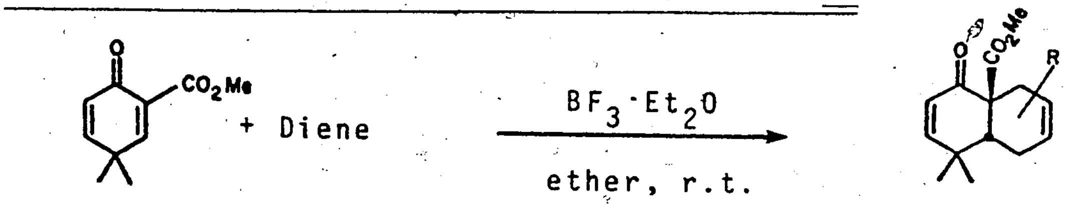
66

(8% yield). Dienone-ester 64 was found to add rapidly to dienes in ether solution and under boron trifluoride etherate catalysis to give 1:1 adducts in good yield as summarized in Table VII. The regiochemistry of the adducts of unsymmetrical dienes was demonstrated by decarboxylation followed by conversion to the ring B aromatic derivatives as summarized in Table VIII.

A. Addition to Butadiene (Entry 14)[58]

When butadiene gas was bubbled into an ether solution of dienone-ester 64 in the presence of boron trifluoride etherate the starting material was rapidly consumed (6 hr.). After workup and chromatographic purification a product was obtained in 70% yield which was shown to be a single compound by cmr analysis (14 lines, Table IX). The mass spectrum showed a molecular ion at m/e 234.1258 indicating the

TABLE VII. Diels-Alder Additions to Dienone-Ester 64



64

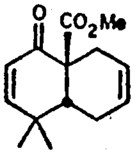
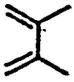
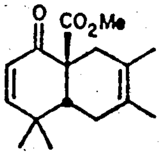
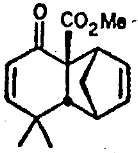
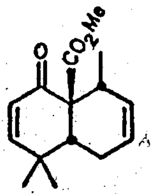
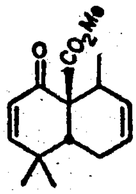
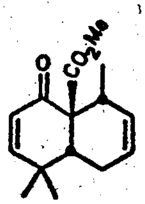
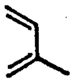
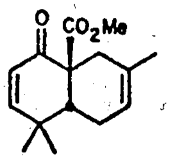
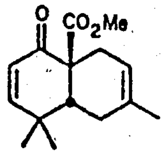
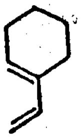
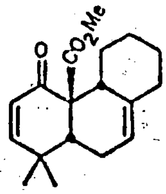
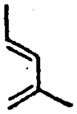
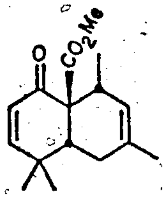
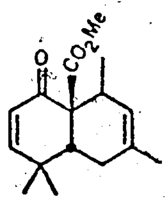
Entry	Diene (equiv.)	Time (hr.)	Yield	Product(s)
14	 (excess)	6	70%	 67
15	 (20)	96	63%	 68
16	 (20)	3	70%	 69
17	 (10)	43	83%[a]	 70
18	 [b] (10)	1.5	74%	  71 (50:50) 70

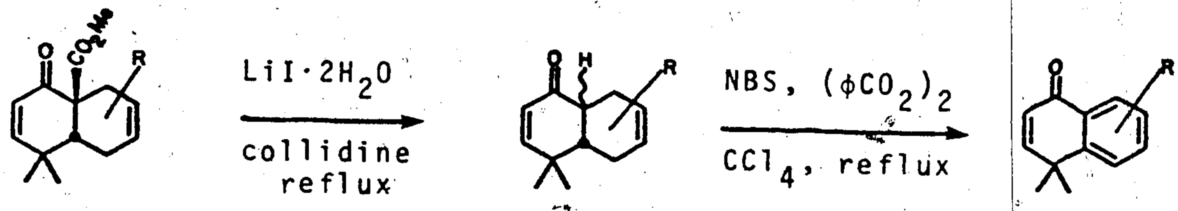
Table VII. (cont'd.)

Entry	Diene (equiv.)	Time (hr.)	Yield	Product(s)
19	 (20)	72	73%	  72 (70:30) 73
20	 (20)	60	87%	 74
21	 (10)	2	83%	  75 (50:50) 76

[a] A small amount (<5% yield) of keto-ester 71 was observed in the unrecrystallized product.

[b] Ferric chloride was used as the catalyst.

TABLE VIII. Derivatization of Adducts of 64 with Unsymmetrical Dienes



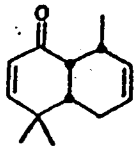
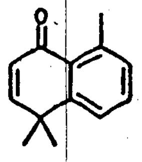
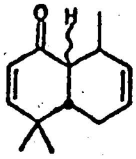
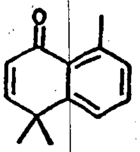
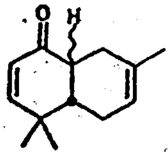
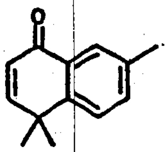
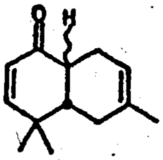
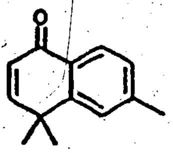
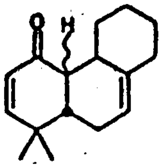
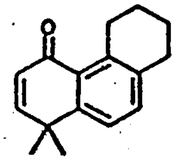
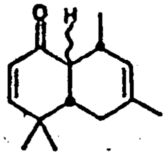
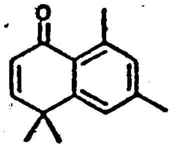
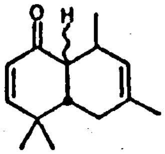
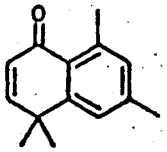
Entry[a]	Adduct	Decarboxylation Product (yield)	Aromatization Product (yield)
17	70	 30 (66%)	 40 (12%)
18	71	 47 & 77 (64%)	 40 (38%)
19a	72	 31 & 36 (97%)	 41 (37%)
19b	73	 48 & 78 (97%)	 49 (43%)

TABLE VIII. (cont'd.)

Entry[a]	Adduct	Decarboxylation Product (yield)	Aromatization Product (yield)
20	74	 32 & 37 (61%)	 42 (20%)
21a	75	 33 & 38 (35%)	 43 (1.7%)[b]
21b	76	 63 & 79 (83%)	 43 (31%)

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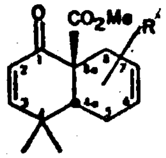
[a] The same entry numbers as Table VII are used for clarity since the results are grouped together in the discussion.

[b] Pure 33 was aromatized.

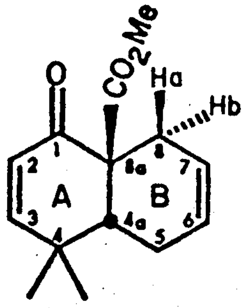
TABLE IX. CMR Shifts (δ) for Some Adducts of Dienone-ester 64



Adduct	67	70	71	72	73	74	75	76
C-1	197.3	196.3	17.0	197.4	197.7	197.6	196.7	197.4
C-2	124.3^a	123.4	124.2^a	124.0	123.9	126.9	125.2^a	124.5^a
C-3	157.8	152.5	157.5	158.0	157.9	155.0	152.6	157.3
C-4	36.2	38.0^a	36.3	36.0	36.2	36.5	37.7	36.4
C-4a	40.8	47.1	42.2	40.4	41.3	43.7	47.4	42.8
C-5	23.9	27.2	24.3	24.2	29.0^a	24.8	32.0	29.1
C-6	124.0^a	127.1	124.5^a	119.3	132.2	116.5	130.3	131.1
C-7	125.5^a	130.5	131.2	131.1	118.5	137.0	127.3^a	125.6^a
C-8	28.6	37.7^a	32.0	33.1	28.7^a	41.5	38.4	32.5
C-8a	56.9	59.3	60.9	57.5	56.6	60.1	59.3	60.6
gem CH_3	30.4 23.8	28.4 27.4	31.3 23.8	30.4 23.6^a	30.4 23.5^b	30.5 25.7	28.5 27.3	31.3 23.7
$-CO_2-$	172.9	174.6	171.6	173.0	173.0	174.3	174.8	171.6
$-O-CH_3$	52.5	52.1	51.9	52.4	52.4	52.4	52.1	51.9
R	--	16.8	16.0	23.4^b	23.4^b	35.3 27.8 26.8 26.4	23.9 17.1	23.1 16.2

[a,b] The precise assignment of these pairs of signals is uncertain.

chemical formula $C_{14}H_{18}O_3$. The ir spectrum showed an absorption at 1730 cm^{-1} characteristic of a saturated ester and a 1663 cm^{-1} band due to an α,β-unsaturated ketone. The nmr spectrum had enone proton signals as doublets (J = 10 Hz) at δ6.57 and 5.87 and two vinyl protons as a multiplet at δ5.66. The spectrum also showed three methyl singlets at δ3.70, 1.18 and 1.07. These spectral data were consistent with the assignment of structure <u>67</u>.



<u>67</u>

The *cis*-stereochemistry of the product was indicated by several factors. Firstly it should be noted that <u>no exceptions</u> to the *cis*-principle are known*. Secondly the nmr spectrum of the adduct (Table X) showed a doublet of doublets (J = 6 Hz, J = 4 Hz) at δ2.75. This signal showed no evidence of a geminal coupling and therefore was assigned to the methine proton at C-4a. The normal chemical shift

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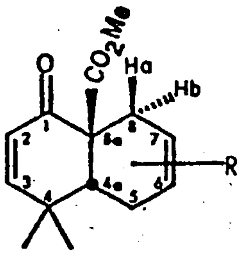
*"Aside from the factors listed...(epimerization of adducts, migration of double bond, reversibility of reaction)...which are independent of the reaction itself and its mechanism, no exceptions are known to the rule that the relative configuration of the starting materials is retained in the adduct; the reliability of the rule is one of the major factors in the importance of the Diels-Alder reaction in synthesis and in stereochemical studies."[6]

TABLE X. NMR Shifts (δ) for Adducts of Dienone-ester 64



Adduct	67[a]	68	69	70	71	72	73	74	75	76
C-2 H	5.87	5.75	5.60	5.72	5.74	5.75	5.75	5.76	5.69	5.81
C-3 H	6.57	6.46	6.31[b]	6.11[b]	6.40	6.43	6.41	6.20	6.09[b]	6.40
C-4a H	2.75	2.63	2.49	2.56	2.63	2.62	2.71	2.56	2.53	2.63
C-5 H	2.11	1.92	3.00	2.10	2.02	2.08	1.91	2.03	complex	1.89
C-6 H	5.66	--	5.05	5.50	5.48	5.29	--	5.16	--	--
C-7 H	5.66	--	5.75	5.35	5.48	--	5.34	--	5.17	5.20
C-8 Ha	2.25	2.09	--	2.70	--	2.08	2.14	2.70	2.65	--
C-8 Hb	2.70	2.47	3.45	--	2.52	2.47	2.62	--	--	2.52
gem CH_3	1.18	1.13	1.27	1.14	1.18	1.16	1.19	1.16	1.10	1.16
	1.07	0.94	1.17	1.10	1.06	1.00	1.02	1.10	1.10	1.02
R	--	1.58	1.60	1.20	1.10	1.66	1.67	complex	1.57	1.64
		1.58	1.41						1.13	1.07

[a] This spectrum was determined in deuteriochloroform.

[b] Long range W-type coupling to C-4a H.

of a proton β to a ketone is δ1.95[46]. It was possible that the proton at C-4a was strongly deshielded by the ester carbonyl group and this was taken as evidence that the ester and the C-4a proton were on the same face of the molecule. Although the preceeding evidence for a *cis*-ring fusion is not absolutely conclusive in this particular case, several examples of this series (Entries 16, 17, 21) give additional nmr evidence which does afford an unambiguous proof. We believe that when coupled with the generality of the *cis*-principle the evidence is sufficient to warrant extrapolation of the stereochemical assignment to the whole series.

B. Addition to 2,3-Dimethylbutadiene (Entry 15)[58]

Dienone-ester 64 reacted smoothly but slowly* (4 days) with 2,3-dimethylbutadiene in the presence of boron trifluoride etherate to produce a single 1:1 adduct in 63% yield. The mass spectrum showed a molecular ion at m/e 262.1568 corresponding to the chemical formula $C_{16}H_{22}O_3$. The ir spectrum showed carbonyl absorptions at 1746 (ester) and 1676 cm^{-1} (enone). The nmr spectrum showed two enone protons as doublets (J = 10 Hz) at δ6.46 and 5.75. Five methyl groups appeared as singlets at δ3.61 (ester), 1.58 (two vinylic methyls), 1.13 and 0.94 (*gem*).

The spectral data were consistent with structure 68. As was the

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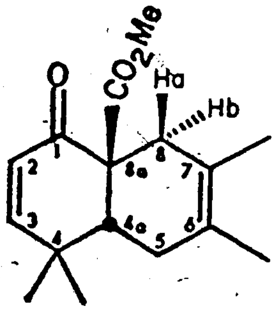
* 2,3-Dimethylbutadiene is a relatively unreactive diene.



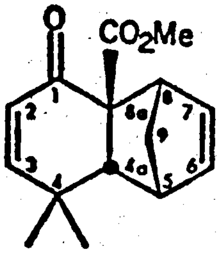
68

case with 67 (Entry 14) the *cis*-stereochemistry was indicated by the deshielding of the proton at C-4a (δ2.63) by the carbonyl of the ester group but the stereochemical assignment was made primarily on the basis of the *cis*-principle supported by the rigorously proven stereochemistry of adducts 69, 70 and 75 (*vide infra*).

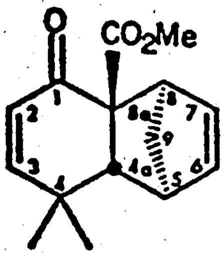
C. Addition to Cyclopentadiene (Entry 16)[58]

Cyclopentadiene reacted rapidly with dienone-ester 64 to give a single 1:1 adduct in 70% yield. The mass spectrum showed a molecular ion at m/e 246.1253 indicating the chemical formula $C_{15}H_{18}O_3$. The ir spectrum showed bands due to a saturated ester (1738 cm^{-1}) and an enone (1662 cm^{-1}) as well as a band at 720 cm^{-1} suggesting a *cis*-disubstituted double bond. The nmr spectrum showed two coupled enone protons (J = 10 Hz) at δ6.31 and 5.60 and two other vinylic protons at δ6.05 and 5.75. Three methyl groups appeared as singlets at δ3.65 (ester), 1.27 and 1.17 (*gem*). The spectral data indicated that addition had occurred at the more substituted double bond. The *cis*-stereochemistry of the fused ring system was unambiguously indicated in this case by the nmr spectrum which showed a long range W-type[47] coupling of 1.5 Hz between the proton at C-3 (δ6.31) and that at C-4a (δ2.49). The required W-configuration of the C-3 and C-4a protons is possible only in the *cis*-fused isomer. As was mentioned previously this W-coupling together with a similar observation for adducts <u>69</u>, <u>70</u> and <u>75</u> was taken as conclusive proof that the *cis*-principle applies to all additions in this series.

Preliminary analysis of the spectral data indicated that the structure of the adduct was either <u>69</u>, which would result from addition to <u>64</u> with secondary overlap with the ketone carbonyl group, or <u>80</u>, which would result from secondary overlap with the ester group

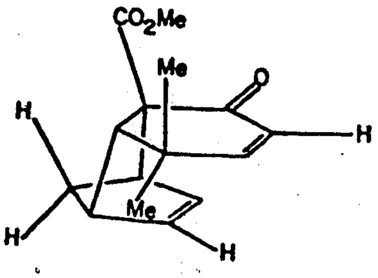


<u>69</u>

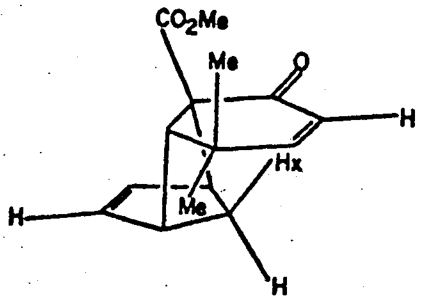


<u>80</u>

of <u>64</u>. A careful examination of molecular models showed that in <u>69</u> the conformation is a "sandwich-like" structure <u>69a</u> in which the isolated double bond was held under the carbon-carbon double bond of the enone system. As a result, the proton of C-2 would be shielded by the isolated double bond and the proton at C-6 would be shielded by the enone double bond. On the other hand in <u>80a</u> one of the C-9 protons (Hx) would be shielded by the enone double bond.



69a



80a

On close examination of the nmr spectrum of the adduct (Table X) it was evident that neither of the C-9 protons (δ1.60 and 1.41) was particularly shielded relative to the bridge protons of the model compound norbornene (δ1.32 and 1.07[45]). Comparison of the chemical shift of the proton at C-2 (δ5.60) with other compounds in this series (δ5.69 to δ5.87) showed that it was experiencing a shielding effect. Furthermore one of the olefinic protons (δ5.75) was shifted upfield from the normal value of δ5.95 for norborene[47]. These data supported the assignment of structure 69 which was in agreement with similar findings in this series that addition of dienes to 64 proceeds with secondary overlap of the enone carbonyl group rather than the ester carbonyl group (*vide infra*, Entries 17, 20, 21).

D. Addition to *trans*-Piperylene (Entry 17)

With *trans*-piperylene under boron trifluoride etherate catalysis, dienone-ester 64 reacted smoothly to give a 1:1 adduct in 83% yield*. The cmr spectrum of the recrystallized product showed that it was a single compound (15 lines, Table IX)**. The mass spectrum showed a molecular ion at m/e 248.1413 characteristic of the chemical formula $C_{15}H_{20}O_3$. The ir spectrum showed a band at 1725 cm^{-1} due to a saturated ester and one at 1685 cm^{-1} indicating an α,β-unsaturated ketone. The nmr spectrum showed two coupled enone protons (J = 10 Hz) at δ6.11

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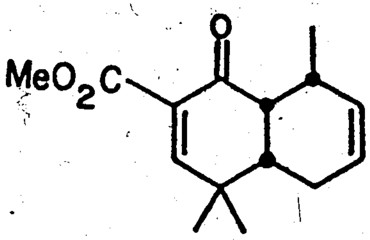
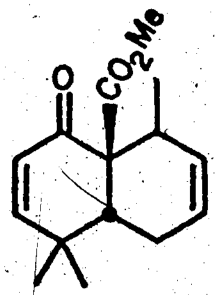
*The keto-ester 81 was also obtained in 6% yield.



81

**Examination of the nmr spectrum of the unrecrystallized product showed a trace (~7% of the adduct) of the isomeric keto-ester 71 identified by comparison with the nmr spectrum of an authentic sample of 71 obtained from addition of *cis*-piperylene to 64 (Entry 18).



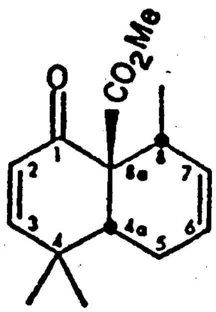
71

and 5.72 and two other coupled vinyl protons (J = 12 Hz) at δ5.50 and 5.35. Methyl signals were observed as singlets at δ3.67, 1.14 and 1.10 and a doublet at δ1.20. These data indicated that the product had been formed by Diels-Alder addition at the more substituted double bond of 64.

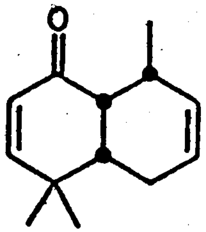
Closer examination of the nmr spectrum of the adduct gave proof of the ring-fusion stereochemistry. The nmr signal of the proton at C-3 (δ6.11) showed a long range W-type coupling[47] of 2 Hz to the proton at C-4a (δ2.56). Inspection of Dreiding models showed that only in the *cis*-fused ring system can these two protons attain the required W-configuration. Again this supported the conclusion that all the adducts in this series are formed in accordance with the *cis*-principle.

The position of the methyl substituent was also indicated by the nmr spectrum. Besides the 2 Hz coupling to the C-3 proton, the signal of the proton at C-4a clearly showed two additional couplings of 11 and 6 Hz. This indicated that two protons were adjacent at C-5 and were only compatible with placement of the methyl substituent at C-8, the result expected for addition according to the *ortho*-rule. If secondary overlap with the enone carbonyl group was preferred in the transition state then we can assign structure 70 to the product of this reaction.

In proof of the position of the methyl substituent, decarboxylation of the adduct with lithium iodide dihydrate in refluxing 2,4,6-collidine[60] fortuitously gave a single product in 66% yield which was identical by nmr and ir analysis with enone 30 obtained by Diels-Alder addition of *trans*-piperylene to 28 (Entry 10). This identity unambiguously fixed the position and stereochemistry of the substituent as that specified by structure 70.



70



30

E. Addition to *cis*-Piperylene (Entry 18)

Dienone-ester 64 reacted with *cis*-piperylene 82 in ether with ferric chloride[*] as a catalyst to give a 50:50 mixture (by nmr integration) of two products in 74% yield. Fractional crystallization gave two isomeric keto-esters, one of which was found to be identical by nmr and ir analysis with keto-ester 70.

The other compound was a single isomer by cmr analysis (Table IX) and showed a molecular ion at m/e 248.1414 ($C_{15}H_{20}O_3$) in the mass spectrum. In the ir spectrum carbonyl bands at 1741 and 1668 cm^{-1} indicated a saturated ester and an enone while an absorption at 702 cm^{-1}

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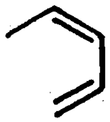
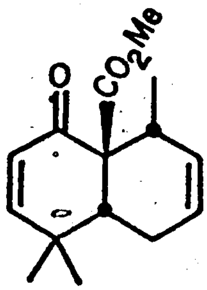
[*] The remarkable acceleration of the rate of Diels-Alder additions to 64 under the catalysis of ferric chloride is discussed later in this chapter.



82

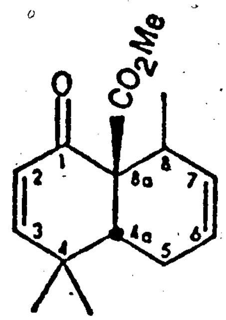


70

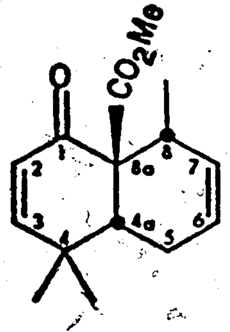
suggested a *cis*-disubstituted double bond. The nmr spectrum showed two enone protons as doublets (J = 10 Hz) at δ6.40 and 5.74 and two other vinyl protons as a singlet at δ5.48. Methyl groups appeared as singlets at δ3.60, 1.18 and 1.06 and a doublet at 1.10.

The *cis*-stereochemistry of the ring fusion was indicated by the appearance of the C-4a proton signal at δ2.70 in the nmr spectrum. As discussed in previous entries the proton is probably deshielded by the ester carbonyl, however the ring fusion stereochemical assignment was made primarily on the basis of the *cis*-principle which was rigorously indicated in this series by the nmr spectra of three examples (69, 70 and 75).

The regiochemistry of the ring B methyl substituent was indicated by the clear presence of two couplings (7 Hz and 4 Hz) in the nmr signal of the C-4a proton. This indicated that C-5 must bear two protons and thus the methyl substituent could only be located on C-8. The preceding evidence indicated that the compound was identical with keto-ester 70 in every structural detail except the stereochemistry at C-8 and thus structure 71 was tentatively assigned.

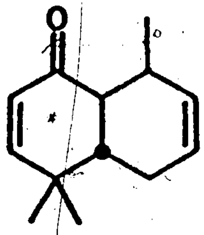


71

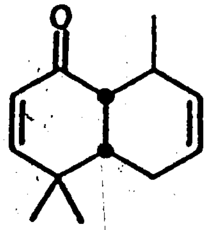


70

The keto-ester 71 was decarbomethoxylated with lithium iodide dihydrate in refluxing 2,4,6-collidine[60] to give a chromatographically inseparable mixture of two enones in 64% yield. The mass spectrum of the mixture showed a molecular ion at m/e 190.1356 indicating the chemical formula $C_{13}H_{18}O$ and the ir spectrum showed an enone absorption at 1671 cm^{-1}. The nmr spectrum showed two sets of signals in an integral ratio of 32:68. The major set of signals included enone protons as doublets (J = 10 Hz) at δ6.60 and 5.77 and a complex vinyl proton signal at δ5.70 to δ5.40. Methyl groups showed up as singlets at δ1.17 and 1.04 and a doublet at δ0.81. The minor set of signals showed coupled enone protons at δ6.27 and 5.70, a complex vinyl signal at δ5.70-5.40 and methyl groups at δ1.30, 1.12 (singlets) and 1.04 (doublet). Comparison of the preceeding nmr data with the spectra of other enones in this series (Table VI) showed that the major set of signals was characteristic of a *trans*-fused enone while the minor set was characteristic of a *cis*-fused enone and structures 47 and 77 were tentatively



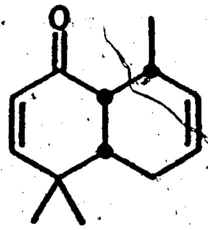
77



47

assigned*.

Conclusive proof of the C-8 stereochemistry of 47 and 77 was offered by the nmr spectrum. As was predicted in the discussion of *cis*-enone 30, the C-8 proton of 47 should be held in the deshielding zone of the carbonyl group while the methyl substituent at C-8 should be unaffected. The C-8 proton of 47 appeared as a multiplet at δ3.06**, strongly deshielded relative to the C-8 proton of 30 (δ2.34). The



30

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* It should be noted that the mixtures 30 + 35 and 47 + 77 are chromatographically separable from each other so that the separation of the precursors 70 and 71 by fractional crystallization is unnecessary for preparative purposes.

** This assignment was confirmed by the observation of significant sharpening of the signal upon irradiation of the protons of the adjacent methyl group (δ1.04).

methyl group at C-8 appeared at the normal value of δ1.04 relative to the deshielded C-8 methyl group of 30 (δ1.38). Such an effect could only occur if the stereochemistry at C-8 was as defined by structure 47. Since 47 and its *trans*-isomer were both derived from the same keto-ester (71), it followed that the *trans*-isomer must have the stereochemistry defined by structure 77.

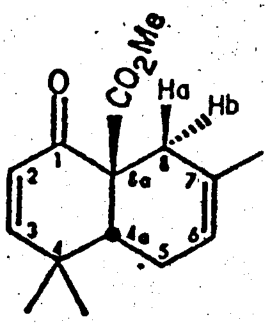
In final proof of the regiochemistry of 71 as well as of 47 and 77 which were derived from it, the mixture of 47 and 77 was aromatized with *N*-bromosuccinimide[42,43] to give an aryl-ketone derivative identical with 40.

F. Addition to Isoprene (Entry 19)

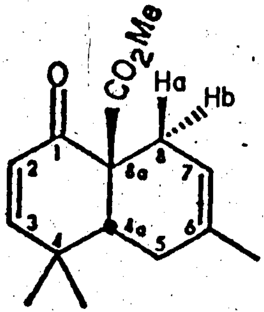
Dienone-ester 64 reacted with isoprene under boron trifluoride etherate catalysis to give a 70:30 mixture (gc analysis) of two isomeric adducts in 73% yield. These two compounds were inseparable by ordinary chromatographic methods and only preparative high-pressure liquid chromatography gave fractions sufficiently enriched in each isomer to allow crystallization. Recrystallization from ether gave pure samples of each adduct. Both isomers were shown to be single compounds by the appearance of 15 lines in their cmr spectra (Table IX).

The major isomer showed a molecular ion at m/e 248.1410 in the mass spectrum indicating the chemical formula $C_{15}H_{20}O_3$ and carbonyl bands in the ir spectrum at 1744 (ester) and 1672 cm^{-1} (enone). The nmr spectrum showed two enone protons as doublets at δ6.43 and 5.75 and a vinyl proton as a multiplet at δ5.29 as well as methyl singlets at δ3.64 (ester), 1.66 (vinylic) 1.16 and 1.00 (*gem*).

The mass spectrum of the minor isomer showed a molecular ion at m/e 248.1412 indicating the chemical formula $C_{15}H_{20}O_3$ and its ir spectrum showed bands at 1740 cm^{-1} indicating a saturated ester and at 1667 cm^{-1} due to an α,β-unsaturated ketone. Its nmr spectrum showed two doublets at δ6.41 and 5.75 due to enone protons and another vinyl proton as a multiplet at δ5.34. Methyl singlets appeared at δ3.67 (ester), 1.67 (vinylic), 1.19 and 1.02 (*gem*). On the basis of the preceeding spectral data and making the ring fusion stereochemical assignment on the basis of the *cis*-principle it is clear that one of the products must be keto-ester 72 and the other must be 73.



72

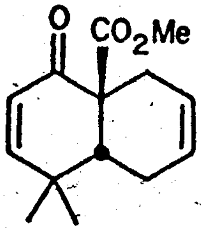


73

The principal signals of the nmr spectra of both compounds (Table X) appeared at virtually identical shifts, however close examination showed significant differences in the protons at C-5 and C-8. The major isomer showed a multiplet at δ2.01 due to the C-5 methylene group and broad doublets at δ2.08 and δ2.47 due to protons

Ha and Hb at C-8. The minor isomer showed a multiplet at δ1.91 due to the C-5 methylene protons and broad doublets at δ2.14 and δ2.62 due to protons Ha and Hb at C-8. We would expect the C-8 protons of 72 to be shielded relative to those of 73 by the proximity of the methyl substituent[46]. Similarly the C-5 protons of 73 would be shielded relative to those of 72. Examination of the preceeding nmr data leads to the conclusion that the major isomer is the *anti-para* addition product 72 while the normal *para*-addition product 73 is the minor component.

This conclusion is supported by the cmr spectra (Table IX). As expected, C-8 of 72 (δ33.1) is deshielded relative to C-8 in 67

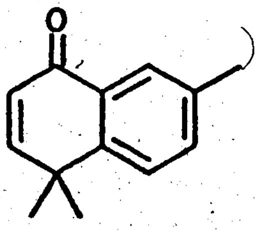


67

(δ28.6) due to the β-effect[61] of the methyl group at C-7 while the C-5 carbons have virtually the same shift (δ24.2 and 23.9). Similarly C-5 in 73 (δ29.0) is deshielded relative to C-5 in 67 (δ23.9) by the β-effect[61] of the methyl substituent at C-6 while the C-8 carbons of each molecule have the same shift (δ28.6 and 28.7).

In absolute proof of the regiochemical assignment the major isomer was converted to the aryl-ketone derivative. Decarboxylation with lithium iodide dihydrate in refluxing 2,4,6-collidine[60] gave a 50:50 mixture (97% yield) of two compounds. The exact mass of m/e 190.1356 ($C_{13}H_{18}O$) and an ir absorption at 1674 cm^{-1} indicated that the mixture consisted of a pair of isomeric enones. Nmr analysis showed signals characteristic of a *cis*-enone: enone doublets at δ6.28 and 5.67 and *gem*-dimethyl singlets at δ1.29 and 1.08. The nmr spectrum also showed signals characteristic of a *trans*-enone: enone doublets at δ6.57 and 5.72 and *gem*-dimethyl singlets at δ1.12 and 1.02.

Aromatization of this mixture of *cis*- and *trans*-enones with *N*-bromosuccinimide[42,43] gave an aryl-ketone derivative (37% yield) identical with the aryl-ketone 41 obtained previously. It follows that the mixture of decarboxylation products must be *cis*- and *trans*-enones 31 and 36 and thus the adduct from which they were derived--the major adduct--must have *anti-para* structure 72.



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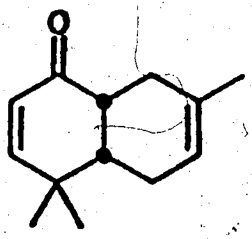

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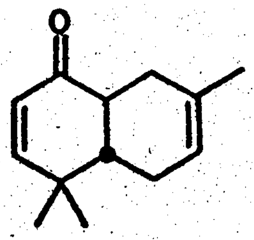

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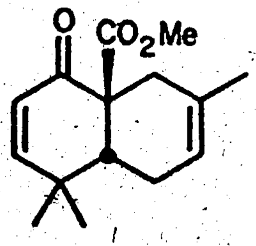
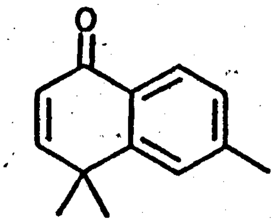


72

By a similar approach the minor isomer <u>73</u> was converted with lithium iodide dihydrate to a 43:57 mixture of two compounds. The mixture gave a molecular ion at m/e 190.1352 in the mass spectrum and showed two enone absorptions at 1686 and 1674 cm^{-1} in the ir spectrum. Nmr analysis showed two sets of signals which were characteristic of a pair of *cis*- and *trans*-enones. The minor set, which was attributed to the *cis*-isomer, included two enone protons as doublets at δ6.29 and 5.68, and a vinyl proton as a multiplet at δ5.33, and methyl singlets at δ1.58, 1.30 and 1.10. The major set, due to the *trans* isomer, included doublets at δ6.56 and 5.72 due to enone protons, a multiplet at δ5.33 due to a vinyl proton, and methyl singlets at δ1.66, 1.14 and 1.04.

The mixture of enones was oxidized with *N*-bromosuccinimide. The aryl-ketone thus obtained gave a molecular ion at m/e 186.1047 indicating the chemical formula $C_{13}H_{14}O$. The ir spectrum showed a band at 1661 cm^{-1} due to an α,β-unsaturated ketone. The nmr spectrum showed two enone protons as doublets at δ6.72 and 6.18, methyl singlets at δ2.40 and 1.44 (six protons) and aryl-proton signals at δ7.95 (*peri*-deshielded), 7.20 and 7.09.

The structure of the aryl-ketone was unambiguously demonstrated by its nmr spectrum. The *peri*-proton at C-8 (δ7.95) appeared as a doublet with a coupling constant of 8 Hz indicating that there is a proton at C-7 and thus the methyl substituent must be at C-6 as shown in <u>49</u> as well as in the enones <u>48</u> and <u>78</u> and the keto-ester <u>73</u> from which all three are derived.



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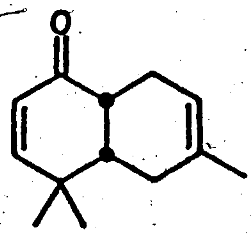

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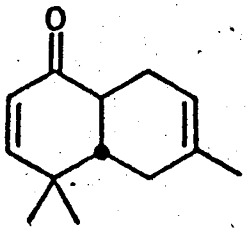
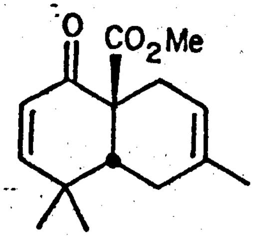


78

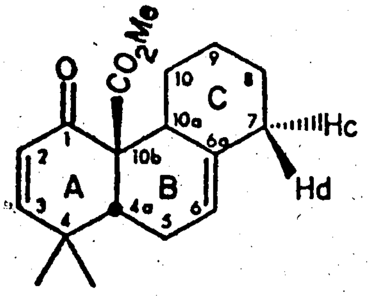


73

G. Addition to 1-Vinylcyclohexene (Entry 20)

1-Vinylcyclohexene (54)[56] reacted smoothly with keto-ester 64 to give a 1:1 adduct in 87% yield. Cmr analysis (Table IX) showed that the adduct was a single compound. The mass spectrum showed a molecular ion at m/e 288.1725 ($C_{18}H_{24}O_3$) and the ir showed bands due to a saturated ester at 1728 cm^{-1}, an enone at 1689 cm^{-1} and a trisubstituted double bond at 835 cm^{-1}. The nmr spectrum showed doublets at δ6.20 and 5.76 due to enone protons and a broad singlet at δ5.16 due to a vinyl proton. Methyl groups appeared as singlets at δ3.66, 1.16 and 1.10.

The preceeding data indicated that Diels-Alder addition had occurred at the more substituted double bond of dienone-ester 64 and, if the addition occurred according to the *cis*-principle and *ortho*-rule and with secondary overlap with the enone carbonyl, structure 74* could be tentatively assigned.



74

The *cis*-stereochemistry of the AB ring fusion was indicated by the appearance in the nmr spectrum of a signal at δ2.56 due to the C-4a proton. As has been discussed previously (Entry 14) this proton was probably deshielded by the ester carbonyl group. Again however this assignment was made primarily on the basis of the inviolate *cis*-principle which was supported in this series with several rigorously proven examples (69, 70, 75).

Decarboxylation of the adduct with lithium iodide dihydrate[60] gave a 47:53 mixture of two compounds in 61% yield. The mixture gave a molecular ion at 230.1674 ($C_{16}H_{22}O$) in the mass spectrum and enone absorptions at 1680 and 1670 cm^{-1} in the ir spectrum. The nmr spectrum

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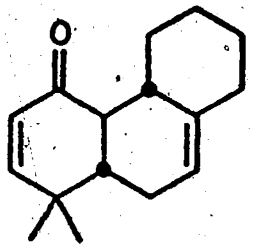
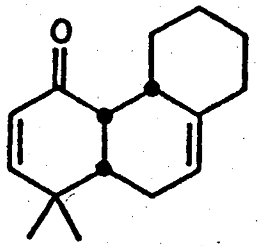
*The numbering scheme shown in structure 74 differs from that recommended by IUPAC and Chemical Abstracts but is used in this chapter to be consistent with other compounds in this series.

showed two sets of signals. The major one was identical with those observed for the pure *trans*-enone 37 and the minor set was identical with the observed spectrum of pure *cis*-enone 32.

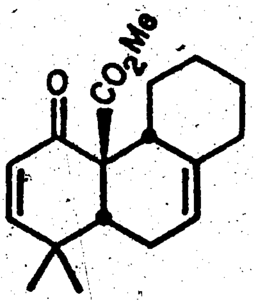


37

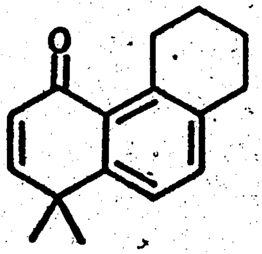


32

The identity of the two products with enones 32 and 37 fixes both the regiochemistry and C-10a stereochemistry of the Diels-Alder adduct as that defined by the structure 74. In confirmation of the regiochemical assignment, aromatization of the mixture of enones with *N*-bromosuccinimide gave an aryl-ketone derivative (20% yield) identical with aryl-ketone 42.



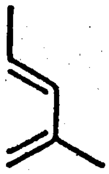
74



42

H. Addition to *trans*-2-Methyl-1,3-Pentadiene (Entry 21)

The boron trifluoride etherate catalysed addition of *trans*-2-methyl-1,3-pentadiene (<u>59</u>) to dienone-ester <u>64</u> proceeded to give a 50:50 mixture (by nmr integration) of two isomeric 1:1 adducts in 83% yield. Separation by fractional crystallization from ether gave two pure adducts each of which was a single compound by cmr (Table IX).

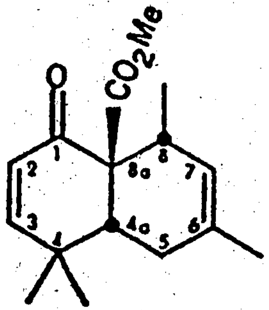


<u>59</u>

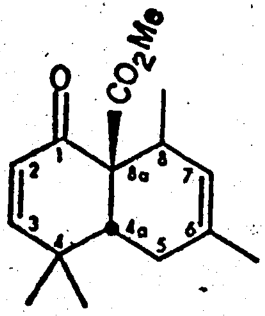
One compound showed a molecular ion at m/e 262.1567 in the mass spectrum indicating the chemical formula $C_{16}H_{22}O_3$. The ir spectrum showed a band due to a saturated ester at 1728 cm^{-1} and an enone absorption at 1689 cm^{-1} as well as a band at 729 cm^{-1} due to a tri-substituted double bond. The nmr spectrum showed two coupled enone protons at δ6.09 and 5.69, a vinyl proton as a multiplet at δ5.17 and give methyl groups as singlets at δ3.64, 1.57 and 1.10 (six protons) and a doublet at δ1.13.

The other compound showed a molecular ion at m/e 262.1574 ($C_{16}H_{22}O_3$) in the mass spectrum and ir absorptions at 1739 (ester) and 1672 cm^{-1} (enone). The nmr spectrum showed doublets at δ6.40 and 5.73 due to two enone protons and a vinyl proton singlet at δ5.23. Methyl singlets appeared at δ3.60, 1.56, 1.16 and 1.02 while a methyl doublet appeared at δ1.07.

Comparison of the principal features of their nmr spectra with keto-esters 70 and 71 (Table IX) suggested that the former product was the expected keto-ester 75 while the latter was the unexpected keto-ester 76. Furthermore the *cis*-ring fusion of 75 was unambiguously indicated by the observation of a long range W-coupling[47] of 2 Hz



75



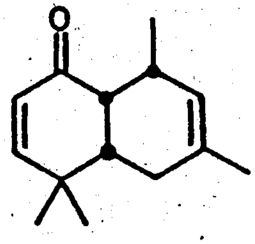
76

between the C-3 (δ6.09) and C-4a (δ2.53) protons. As stated previously, the required W-configuration is only possible in the stable conformation of the *cis*-isomer and not in the *trans*-isomer. The *cis*-fusion of 76, which did not show a W-coupling, was assigned on the strength of the *cis*-principle as discussed for other examples in this series.

The regiochemistry of both isomeric keto-esters was indicated after close examination of their nmr spectra. The signal due to the C-4a proton of 75 (δ2.53) showed two additional couplings of 10 and

6 Hz and the C-4a proton of 76 showed up as a doublet of doublets at δ2.63 with coupling constants of 10 and 4 Hz. In each case the indicated presence of two protons on C-5 required that a methyl substituent be placed at C-8 and consequently the allylic methyl substituent must be at C-6.

The structure of adduct 75 was confirmed by decarbomethoxylation with lithium iodide dihydrate[60] to give a 65:35 mixture of two products. Nmr analysis of this mixture showed a major set of signals which was identical with the spectrum of pure *cis*-enone 33. The minor set of signals was found to be identical with the spectrum of pure *trans*-enone 38. This result fixes both the regiochemistry and the C-8 stereochemistry of keto-ester 75 as that illustrated by the structure.



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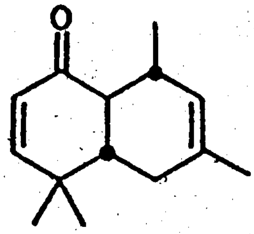
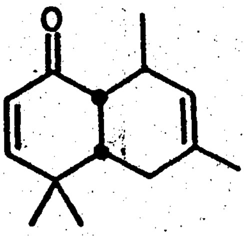
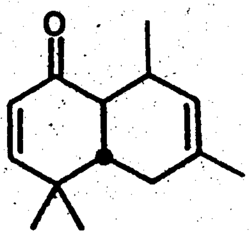


38

Using a similar approach the keto-ester 76 was decarboxylated with lithium iodide dihydrate[60] to give a 55:45 mixture of two products in 83% yield. The mass spectrum of the mixture showed a molecular ion at m/e 204.1518 ($C_{14}H_{20}O$) and the ir spectrum showed enone absorptions at 1681 and 1670 cm^{-1}. The nmr spectrum showed two sets of signals. The major one was characteristic of a *cis*-fused enone (Table VI) with coupled enone protons at δ6.25 and 5.67, a vinyl proton doublet at δ5.38 and methyl groups at δ1.56, 1.28, 1.11 (singlets) and 0.97 (doublet). The minor set of signals was characteristic of a *trans*-fused enone (Table VI). Enone protons appeared as doublets at δ6.57 and 5.73 and a vinyl proton appeared as a multiplet at δ5.23. Methyl groups appeared at δ1.64, 1.16, 1.02 (singlets) and 0.75 (doublet). The preceeding spectral data supported the tentative assignment of the *cis*- and *trans*-enones as structures 63 and 79*.



63



79

Conclusive evidence of the C-8 stereochemistry of both the enones and the keto-ester 76 was offered after close examination of the nmr spectrum of 63 and 79. As was predicted in the discussion of Entry 13 the C-8 proton of *cis*-enone 63 was deshielded by the ketone carbonyl

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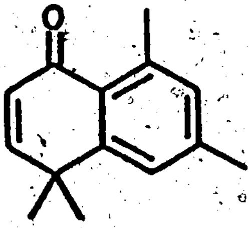
*This assignment was confirmed by irradiation of the methyl doublet at δ0.97 which produced a marked sharpening of the multiplet at δ2.97.

and appeared at $\delta 2.97^*$ while the C-8 methyl substituent appeared at the normal shift of $\delta 0.97$. Such an effect is only possible if the C-8 stereochemistry is as depicted in 63.

In proof of the regiochemistry, the mixture of enones 63 and 79 was aromatized with *N*-bromosuccinimide to give an aryl-ketone derivative in 31% yield which was identical with the aryl-ketone 43 obtained previously (Entry 13).



43

From the preceeding results it can be seen that dienone-ester 64 is a much more reactive dienophile than dienone 28 and reacts even with relatively unreactive dienes (Entry 15) to give adducts in good yields. Furthermore the dienophilicity (with one minor exception, Entry 17) is almost entirely restricted to the more substituted double bond. As expected the *ortho*-rule is followed when applicable (Entries 17, 18, 20 and 21). However the anticipated promotion of

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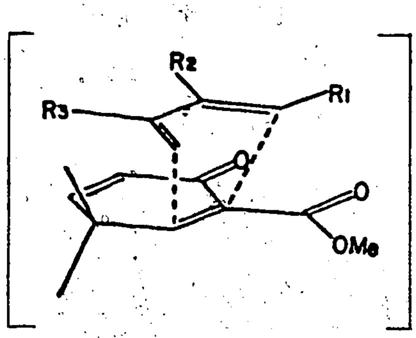
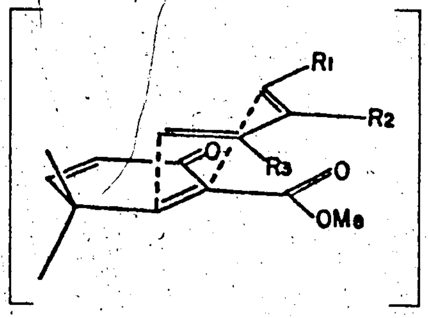
[*] It should be noted that the mixtures 33 + 38 and 63 + 79 are chromatographically separable from each other so that the separation of 75 and 76 by fractional crystallization is unnecessary for preparative purposes.

para-addition of 2-substituted dienes under boron trifluoride etherate catalysis was disappointingly small (Entry 11). The *endo*-selectivity of additions to dienone-ester 64 appears to be with a dominant preference for secondary overlap[15] with the ketone carbonyl group (transition states of type A) rather than with the ester group (transition states of type B) (Entries 17, 18 and 20).



A



B

One particularly interesting observation however was the formation of the two C-8 epimeric adducts 75 and 76 by addition of *trans*-2-methyl-1,3-pentadiene (59)*. These two products clearly result from addition via two quite different transition states. Keto-ester 75 would be the result of addition via transition state 75A whereas keto-ester 76 would be the result of addition via transition state

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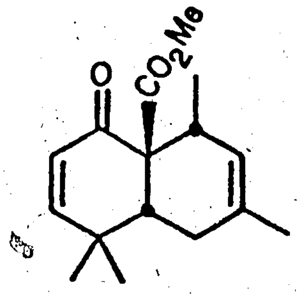
*The formation of a pair of epimeric adducts 70 and 71 (74% yield, 50:50 ratio) from addition of *cis*-piperylene probably stems at least partly, if not entirely, from the presence of *trans*-piperylene (~3%) as an impurity in the commercial *cis*-piperylene used. *trans*-Piperylene is a much more reactive diene than the *cis*-isomer and could compete effectively for the dienophile. The twenty-fold molar excess of diene used would provide sufficient *trans*-piperylene for conversion of up to ~60% of the dienophile to 70.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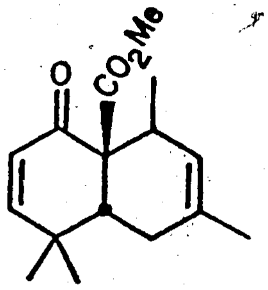
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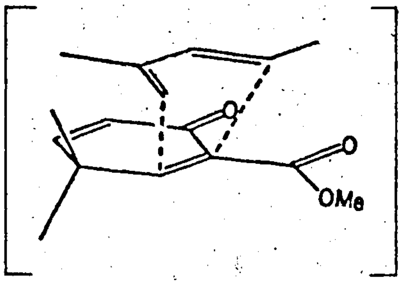
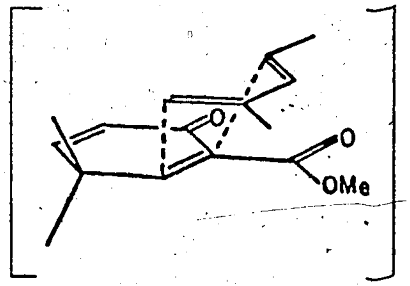
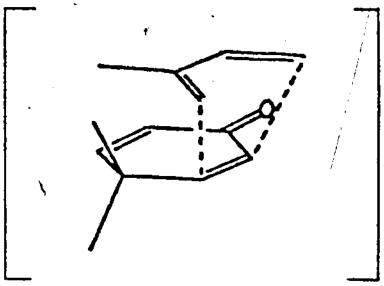
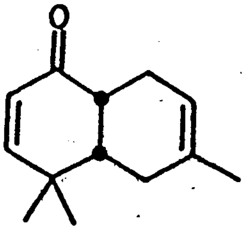

75A


76B

76B. The competition of these two transition states is attributed to a destabilization of transition state 75A by steric interaction between the C-2 methyl group of the diene and a C-4 methyl group of the dienophile. This steric effect is analagous to that encountered in the addition of isoprene to dienone 28 (Entry 11). In that case steric destabilization of the transition state 48A leading to the electronically favoured product 48 resulted in the exclusive formation of product 31 via the electronically disfavoured *anti-para* transition state 31A. In the case of addition of *trans*-2-methyl-1,3-pentadiene (59) the combined *ortho-* and *para-*directing electronic effects are



48A



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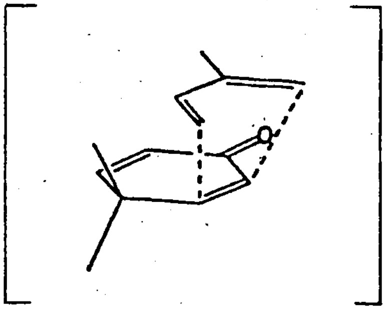
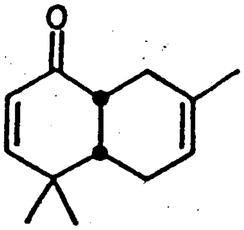


31A



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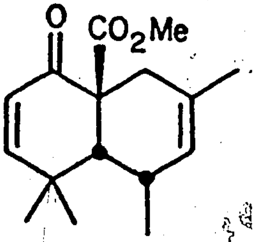
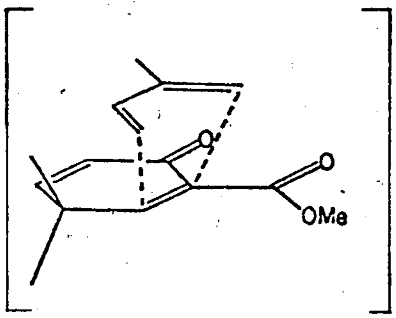
sufficient to overcome the steric destabilization of transition state 75A. Thus no abnormal addition product 82 is observed.



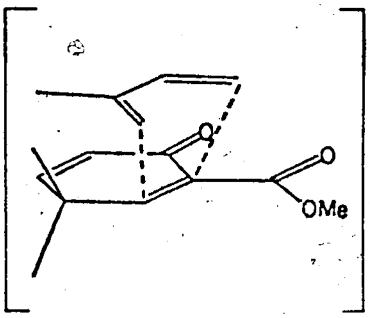
82

However, the steric destabilization in transition state 75A can be alleviated without violation of the *ortho*- and *para*-rules in this case by addition via transition state 76B in which no such steric interaction can occur. The experimental results confirm that this transition state does in fact compete effectively with 75A.

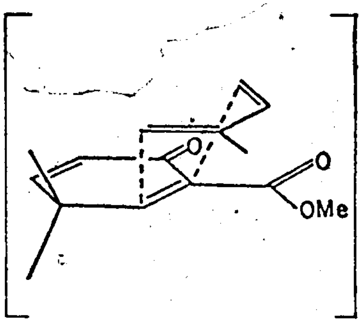
The competition of the two different transition states 75A and 76B for addition of *trans*-2-methyl-1,3-pentadiene (59) suggests that a similar effect might operate for addition of isoprene. A portion of the material would proceed via the *para*-rule guided transition state 73B, in which there is no steric interaction between the methyl groups, to give only keto-ester 73. The remainder would proceed via transition state 72A/73A through which the ratio of products 72 and 73 would be governed by the relative strengths of the steric and electronic directing effects.



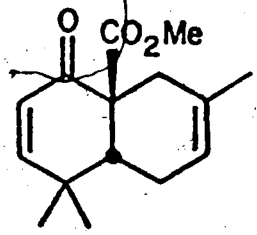
72A



73A



73B



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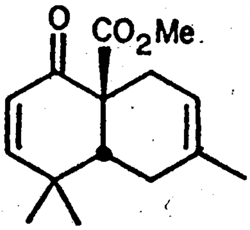
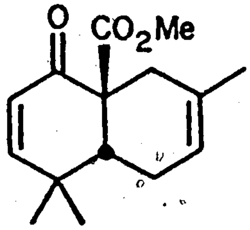


73

In view of the preceeding discussion two possible methods are evident for further enhancement of the *para*-selectivity of addition of isoprene to dienophiles of this type. Increasing the polarization of the dienophilic double bond should lead to increased *para*-selectivity regardless of which transition state (A or B) is in effect. And secondly, any change in the reaction conditions which would favour a transition state of type B relative to one of type A should also increase the *para*-selectivity since only *para*-addition of isoprene is expected via transition states of type B. The former requirement might be achieved either by the use of a stronger (and therefore more electron withdrawing) Lewis acid catalyst or by substitution of the carbomethoxyl group of 64 with a more electron withdrawing substituent. Thus the ratio of *para*:*anti-para* addition products could well be a function of the relative Lewis acidities of a series of catalysts. With regard to the latter requirement it should be emphasized that *endo*-selectivity is increased under the influence of Lewis acid catalysis[17,36]. Thus one might predict that appropriate choice of a Lewis acid which would, in the ideal case, complex only with the ester carbonyl would promote preferential secondary overlap with the ester group (as in B) rather than with the ketone carbonyl (as in A).

To study these possibilities we examined a variety of Lewis acids as catalysts for the addition of isoprene to dienone-ester 64 in ether solution and also briefly examined the reaction under thermal conditions. The results are summarized in Table XI. The table shows that the increase in the proportion of *para*-addition product obtained by varying the catalyst does not strictly parallel the general order of Lewis acidity[62]: $BX_3>AlX_3>FeX_3>SbX_5>SnX_4>ZnX_2$. It appears that the results are complicated by other factors, most probably the effect of the relative hardness or softness[64] of the Lewis acids.

Several entries are particularly noteworthy. Firstly the catalytic effect of boron trifluoride (Entry 19) actually acts to decrease the *para*-selectivity of the reaction relative to the thermal cases (Entries 22 and 23). This is almost certainly due to the effect of preferential coordination of the relatively hard Lewis acid--boron trifluoride--with the ketone carbonyl group. The result is promotion of transition state <u>72A</u>/<u>73A</u> in which the electron withdrawing effect on the dienophilic double bond promoting *para*-rule guided addition is insufficient to counteract the steric directing effect which promotes *anti*-*para* addition. Thus the predominant product is <u>72</u> rather than <u>73</u>.



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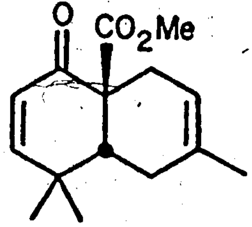
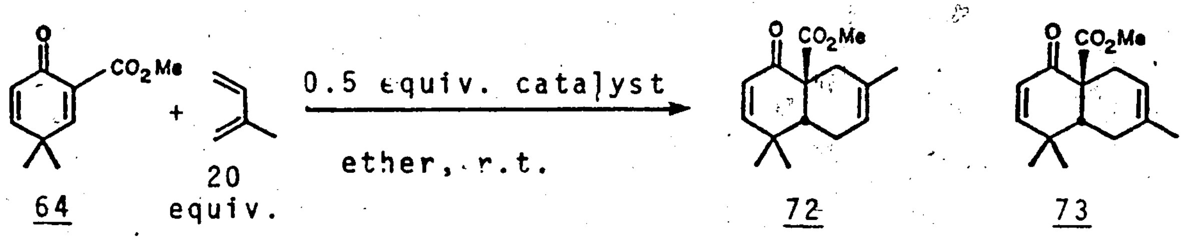


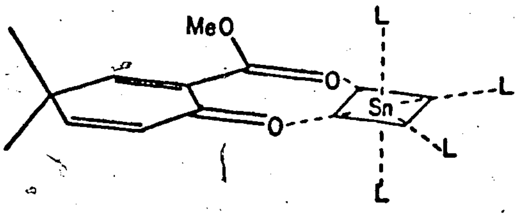
<u>73</u>

TABLE XI. Effect of Catalysts on Addition of Isoprene to Dienone-ester 64



Entry	Catalyst	Time for completion (hr.)	Yield	73:72
19	$BF_3 \cdot Et_2O$	72	73%	30:70
22	125° toluene			40:60
23	250° mesitylene			47:53
24	$TiCl_4$	14		48:52
25	$ZnCl_2$	48		48:52
26	$FeCl_3$	0.3		50:50
27	$SnBr_4$[63]	168		51:49
28	$AlCl_3$	4		53:47
29	$AlBr_3$	265	64%	56:44
30	$SbCl_5$	4		66:34
31	$SnCl_4$	44	99%	82:18

In the case of stannic chloride (Entry 31) the Lewis acid is capable of forming 1:2 complexes with certain Lewis bases such as aldehydes, ketones, esters and ethers[65]. This could result in the formation of a complex such as 83 (L = ligand: Cl^-, OCR_2, and/or OR_2) between the Lewis acid and the bidentate ligand dienone-ester 64.



83

The electron withdrawing effect of the Lewis acid exerted on the dienophilic double bond through the two carbonyl groups at once, together with the expected increase in contribution to the reaction from transition state 73B* could account for the surprisingly large 73:72 product ratio. Regardless of the reason for this effect, the ability to select the predominant product of addition (72 or 73)

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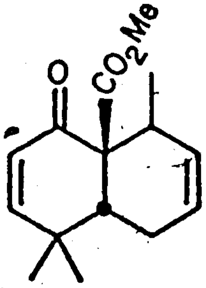
*This increase is expected for two reasons. Firstly, Lewis acid complexation of the ester carbonyl to any extent would be expected to promote secondary overlap with ester group[17,36] at the expense of secondary overlap with the ketone. And secondly, since the experimental evidence suggests (Entry 19) that the hard Lewis acid boron trifluoride complexes preferentially with the ketone carbonyl, it is possible that the very soft Lewis acid stannic chloride might exhibit a preference for closer association with the ester carbonyl in complex 83. This would further promote secondary overlap with the ester relative to the ketone and lead to an increased contribution to the reaction from 73B.

solely by the choice of the Lewis acid catalyst (boron trifluoride etherate or stannic chloride) constitutes a prime example of the concept of "guidance by catalysis" which has been conceived and demonstrated by Valenta[66,67]. The realization of this capability for product selection constitutes a powerful tool in the design of synthetic schemes.

The case of ferric chloride (Entry 26) is also noteworthy. The remarkable increase in reaction rate brought about by this catalyst has made possible the addition to 64 of the relatively unreactive diene *cis*-piperylene (Entry 18) to give keto-ester 71 and has also allowed the rapid generation of adduct 74 in good yield with efficient use (less than two equivalents required) of the rather costly diene 1-vinylcyclohexene (54) (see Chapter 3 of this thesis).



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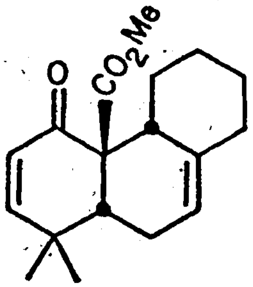

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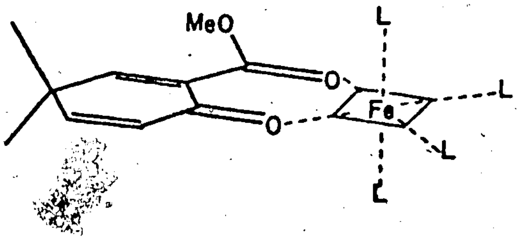
The reasons for this effect could stem from the ability of Fe(III) to form hexacoordinate complexes[68] with β-dicarbonyl compounds, so that the bidentate ligand keto-ester 64 could form a complex such as 84 (L = ligand: Cl^-, OCR_2 and/or OR_2) as was suggested for stannic



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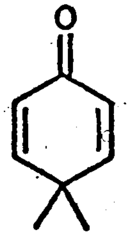
chloride. The electron withdrawing effect of the Lewis acid acting through both carbonyls could lead to a particularly strong polarization of the double bond. Since ferric chloride is expected[62] to be a stronger Lewis acid than stannic chloride the slower rate for stannic chloride is not considered unusual.

The loss of *para*-selectivity of addition is puzzling however. The greater induced polarization of the dienophilic double bond by ferric chloride should be expressed in the product ratio. Possibly the lack of selectivity is the result of a kinetic control on the extremely fast reaction which does not allow selection of the orientation leading to the most stable transition state. The use of a lower reaction temperature might bring out this selectivity (if present) by allowing thermodynamic factors to affect the development of the transition state.

In conclusion, the development of dienone 28 and dienone-ester 64 as dienophiles makes available two useful new intermediates for the synthetic chemist. In particular dienone-ester 64 offers a reactive dienophile which can add efficiently even to relatively unreactive dienes. Furthermore the activating substituent (carbomethoxyl) of 64 can either be removed or used as reactive site for further elaboration of the adducts.



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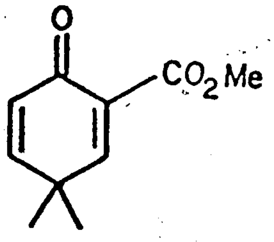
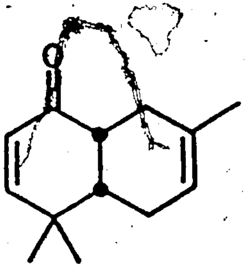


64

Having demonstrated the feasibility of generating Diels-Alder adducts of dienone 28 and dienone-ester 64 we have undertaken to demonstrate the synthetic utility of several of these adducts. The use of enone 31 in the total synthesis of ionene[43] has already been described while the use of keto-esters 73 and 74 will be illustrated in subsequent chapters of this thesis.



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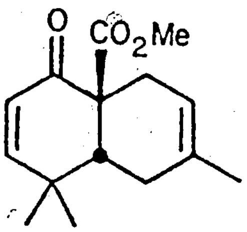

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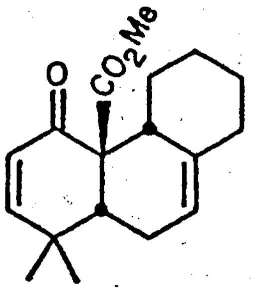

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Experimental

General

Melting points were determined on a Kofler hot stage apparatus and are uncorrected. Elemental analyses were performed by the microanalytical laboratory of this department. Infrared (ir) spectra were recorded on a Perkin-Elmer model 457 or Nicolet 7-199 FT-IR spectrophotometer and, except where otherwise stated, were obtained on solutions in chloroform. Proton nuclear magnetic resonance (nmr) spectra were recorded on a Varian HA-100, HA-100/Digilab or Bruker WH-200 spectrometer and, except where otherwise stated, were obtained on solutions in carbon tetrachloride with tetramethyl silane as internal reference. Carbon-13 nuclear magnetic resonance (cmr) spectra were recorded on a Bruker WP-60/Nicolet BNC-12 system or a Bruker HFX-90/Nicolet 1085 system and were obtained on solutions in deuteriochloroform using tetramethylsilane as internal reference. CMR data on compounds 23, 30-33, 35-37, 67, and 70-76 of Chapter 1 are reported either in this section or in Table VI or IX of Chapter 1. The following abbreviations are used: s = singlet, d = doublet, t = triplet, q = quartet and m = multiplet. Mass spectra (ms) were recorded using A.E.I. model MS9, MS12 or MS50 mass spectrometers. Gas chromatography (gc) was performed on a Hewlett Packard 5750 research chromatograph using stainless steel columns (8' × 1/8") packed with either 10% diethylene-glycol succinate (Column A) or 15% SE-30 (Column B) on 80-100 mesh Chromosorb W, acid washed and treated with dimethylchlorosilane. Unless stated otherwise anhydrous magnesium sulfate was used for drying organic solutions.

Materials

Benzene was distilled over lithium aluminum hydride or sodium wire. Pyridine was distilled over barium oxide and stored over potassium hydroxide pellets. 2,4,6-Collidine was distilled over potassium hydroxide pellets. Isoprene was distilled prior to use. Boron trifluroide etherate was distilled over calcium hydride according to the procedure of Brown[69,70]. Nitrogen was passed through a purification train of Fieser's solution[70], saturated aqueous lead acetate, concentrated sulfuric acid, and potassium hydroxide pellets. 4,4-Dimethyl-2,5-cyclohexadien-1-one 28 was prepared from 4,4-dimethyl-2-cyclohexen-1-one 23 by the method of Zimmerman[41]. 4,4-Dimethyl-2-cyclohexen-1-one was prepared from methyl vinyl ketone and *N*-(1-isobutenyl)-piperidine by the method of Djerassi[39]. *N*-(1-Isobutenyl)-piperidine was prepared by the method of Benzing[71]. Vinylcyclohexene was prepared according to the established procedure[55] however a more efficient method of preparation is described in Chapter 3 of this thesis.

General Conditions for Diels-Alder Reactions of Enone 23 (Table I)

Enone 23 was dissolved in the specified solvent (~1% solution) and the specified quantity of catalyst was added. Then the specified quantity of diene was added as a solution in the specified solvent (except in the case of butadiene (Entry 7) which was bubbled slowly into the solution). The reaction mixture was then maintained at the specified temperature for the time specified. The mixture was cooled to room temperature and saturated aqueous sodium bicarbonate was added. The mixture was extracted with ether or chloroform and the extracts were washed with water, dried, filtered and concentrated. Column chromatography on silica gel eluting with ether/petroleum ether gave the products as specified in Table I. The mixture of ketones 24 and 25 (~50:50) showed the following spectral properties: nmr δ7.15, 6.46, 6.30 (all d, 2H total, all J = 10 Hz, 2X-HC=C$\underline{H}$-C$(CH_3)_2$), 5.86, 5.76, 5.66 (all d, 2H total, all J = 10 Hz, 2X-$\underline{H}$C=C-C$(CH_3)_2$), 1.13 and 1.06 (both s, 12H total, 4X-CH_3); ir (neat) 1660 (C=0), 1379 and 1369 cm^{-1} (CH_3); ms M^+ 230. Ketone 27 showed the following spectral properties: nmr δ5.33 (m, 1H, =CH-) 2.08 (s, 3H, CH_3-CO-), and 1.63 (br s, 3H =C-CH_3); ms M^+ 138.

4,4-Dimethyl-4aβ,5,8,8aβ-tetrahydro-1(4*H*)-naphthalenone (29)*

Dienone 28[41] (306 mg, 2.51 mmol) was dissolved in ether (20 ml, distilled over lithium aluminum hydride) under an atmosphere of nitrogen. Boron trifluoride etherate (179 mg, 1.26 mmol) was added to the stirred solution and after 15 min. dry butadiene gas (passed through a drying

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*The stereochemical designations used in this and all other chemical names used in this section denote relative stereochemistry. All compounds used and obtained were racemic.

tube of anhydrous calcium chloride) was bubbled into the solution. Additional butadiene gas was introduced for 15 min. each day for 22 days. Then saturated aqueous sodium bicarbonate (3 ml) was added and the reaction mixture was extracted with methylene chloride. The extracts were washed with water, dried, filtered and concentrated. Column chromatography of the residue on silica gel, eluting with 2% ether in petroleum ether, gave enone <u>29</u> (78 mg, 26% yield based on consumed starting material) which crystallized on standing. Further elution with 10% ether in petroleum ether gave recovered dienone <u>28</u> (99 mg, 31% recovery). Molecular distillation of chromatographically pure enone <u>29</u> in a Kugelrohr apparatus gave pure crystals of enone <u>29</u>: mp 69.5 - 70.5°C; nmr δ6.31 (dd, 1H, J = 10, J' = 2 Hz, -C<u>H</u>=CH=CO-), 5.72 (d, 1H, J = 10 Hz, -CH=C<u>H</u>-CO-), 5.55 (m, 2H, -CH=CH-), 2.92 (m, 1H, -$\overset{|}{\text{C}}$H-CO-), 2.83 (dm, 1H, J = 18 Hz, C-8 Hb), 1.99 (m, 3H, C-4a H and C-5 -CH_2-), 1.94 (dm, 1H, J = 18 Hz, C-8 Ha), 1.31 (s, 3H, CH_3), and 1.10 (s, 3H, CH_3); ir (CCl_4) 1675 (C=O), 1383, and 1371 cm^{-1} (CH_3); ms M^+ 176.1202 (calcd. for $C_{12}H_{16}O$: 176.1202). <u>Anal.</u> Calcd. for $C_{12}H_{16}O$: C 81.77, H 9.15; Found: C 81.83, H 9.29.

<u>Equilibration of 4,4-Dimethyl-4aβ,5,8,8aβ-tetrahydro-1(4H)-naphthalenone (29) and 4,4-Dimethyl-4aβ,5,8,8aα-tetrahydro-1(4H)-naphthalenone (34).</u>

A mixture of *cis*- and *trans*-enones <u>29</u> and <u>34</u>* (43:57 by nmr

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*This mixture was obtained in 78% yield by decarboxylation of keto-ester <u>67</u> under conditions similar to those used for decarboxylation of keto-esters <u>70</u> through <u>76</u> (*vide infra*).

integration, 202 mg, 1.15 mmol) was dissolved in methanol (10 ml) and 1.0 N aqueous sodium hydroxide (10 ml) was added. After stirring for 26 hr. the mixture was extracted with methylene chloride. The extracts were washed with water, dried, filtered and concentrated. Column chromatography of the residue on silica gel, eluting with 2% ether in petroleum ether, gave a mixture of *cis*- and *trans*-enones 29 and 34 (145 mg, 72% yield) in a 33:67 ratio as determined by gc analysis (Column B). Nmr analysis of this mixture showed two distinct sets of signals. The minor set was identical with the spectrum of pure *cis*-enone 29 while the major set was attributable to *trans*-enone 34: nmr δ6.58 (d, 1H, J = 10 Hz, -CH=CH-CO-), 5.82 (d, 1H, J = 10 Hz, -CH=CH-CO-), 5.62 (m, 2H, -CH=CH-), 1.13 (s, 3H, CH_3), and 1.04 (s, 3H, CH_3). The following data were recorded for the mixture: ir (neat) 1680 (C=O), 1381, 1369 (CH_3), 670 cm^{-1} (HC=CH, *cis*); ms M^+ 176.122 (calcd. for $C_{12}H_{16}O$: 176.1201).

4,4,8α-Trimethyl-4aβ,5,8,8aβ-tetrahydro-1(4H)-naphthalenone (30).

Dienone 28 (116 mg, 0.935 mmol) was dissolved in ether (10 ml, distilled over lithium aluminum hydride) under an atmosphere of nitrogen. Boron trifluoride etherate (66 mg, 0.468 mmol) was added and, after 15 min., *trans*-piperylene (1.27 g, 18.7 mmol) was added. The solution was stirred for 6 days after which a solution of *trans*-piperylene (639 mg, 9.4 mmol) in ether (5.0 ml) was added and the mixture stirred for an additional 2 days. Saturated aqueous sodium bicarbonate solution ([illegible] ml) was added and the mixture was extracted with methylene chloride. The extracts were washed with water, dried, filtered and concentrated. Column chromatography of the residue on silica gel, eluting with 2-3% ether in petroleum ether, gave enone <u>30</u> (123 mg, 69% yield) which crystallized on standing: mp 50 - 54°C; nmr δ6.15 (dd, 1H, J = 10, J' = 1.5 Hz, $-C\underline{H}=CH-CO-$), 5.58 (d, 1H, J = 10 Hz, $-CH=C\underline{H}-CO-$), 5.51, 5.37 (both dm, total 2H, J = 12 Hz each, $-C\underline{H}=C\underline{H}-$), 2.86 (dd, 1H, J = 4, J_2 = 3Hz, $-\overset{|}{C}H-CO-$), 2.34 (m, 1H, $-\overset{|}{C}\underline{H}-CH_3$), 2.10, 1.94 (each d, 2H, each J = 16 Hz, $-C\underline{H_2}-CH=CH-$), 1.38 (d, 3H, J = 8 Hz, $-\overset{|}{C}H-C\underline{H_3}$), 1.33, (s, 3H, CH_3), and 1.10 (s, 3H, CH_3); ir 1686 (C=O), 1397, 1386 (CH_3), and 716 cm^{-1} (*cis* CH=CH); ms M^+ 190.1359 (calcd. for $C_{13}H_{18}O$: 190.1358). <u>Anal.</u> Calcd. for $C_{13}H_{18}O$: C 82.06, H 9.54; Found: C 81.68, H 9.56.

<u>4,4,8α-Trimethyl-4aβ,5,8,8aα-tetrahydro-1(4H)-naphthalenone (35) and 3β-Methoxy-4,4,8-trimethyl-3,4,4aβ,5,8,8aα-hexahydro-1(2H)-naphthalenone (44).</u>

Enone <u>30</u> (108 mg, 0.57 mmol) was dissolved in methanol (5.0 ml) and an aqueous 1.0 N solution of sodium hydroxide (1.0 ml) was added with stirring. After 20 hr. the reaction mixture was extracted with methylene chloride and the extracts were washed with water, dried, filtered and concentrated. Column chromatography of the residue on silica gel eluting with 2-3% ether in petroleum ether gave pure *trans*-enone <u>35</u> (69 mg, 64% yield) as an oil: nmr 6.49 (d, 1H, J = 10 Hz, $-C\underline{H}=CH-CO-$), 5.72 (d, 1H, J = 10 Hz, $-CH=C\underline{H}-CO-$), 5.58, 5.41 (each dm, total 2H, each J = 12 Hz, $-C\underline{H}{=}C\underline{H}-$), 2.44 (m, 1H, $-\overset{|}{C}\underline{H}-CH_3$), 1.19 (d, 3H, J = 6 Hz, $-\overset{|}{C}H-C\underline{H}_3$), 1.14 (s, 3H, CH_3), and 1.06 (s, 3H, CH_3); ir 1677 (C=O), 1660 (C=C), 1374, 1360 (CH_3), and 690 cm^{-1} (*cis* CH=CH); ms M^+ 190.1360 (calcd. for $C_{13}H_{18}O$: 190.1358). Anal. Calcd. for $C_{13}H_{18}O$: C 82.06, H 9.54; Found: C 82.16, H 9.78. Further elution with 2-3% ether in petroleum either gave methoxy-ketone 44 (32 mg, 26% yield): nmr δ5.51, 5.33 (each dm, total 2H, each J = 10 Hz, $-\underline{H}C{=}C\underline{H}-$), 3.26 (s, 3H, $-OCH_3$), 3.18 (dd, 1H, J = J' = 3 Hz, $-\overset{|}{C}\underline{H}-OCH_3$), 2.55 (d, 2H, J = 3 Hz, $-CH_2-CO-$), 1.07 (s, 3H, CH_3) 1.03 (s, 3H, CH_3), and 0.97 (d, 3H, J = 6 Hz, $-\overset{|}{C}H-C\underline{H}_3$); ir 1714 (C=O), 1383, 1360 (CH_3), and 683 cm^{-1} (HC=CH); ms M^+ 222.

4,4,8-Trimethyl-1(4$\underline{H}$)-naphthalenone (40)

Enone 30 (85 mg, 0.45 mmol) was dissolved in carbon tetrachloride (10 ml) and *N*-bromosuccinimide (159 mg, 0.89 mmol) and benzoyl peroxide (5.0 mg, 0.041 mmol) were added. The mixture was heated at reflux with stirring for 30 min., then cooled to room temperature, filtered and concentrated. Column chromatography of the residue on silica gel, eluting with 1% ether in petroleum ether, gave an impure sample of aryl ketone 40. A second chromatographic purification of this material provided a pure sample of aryl ketone 40 (10 mg, 12% yield): nmr δ7.30 (d, 2H, J = 4 Hz, C-5 H and C-7 H), 7.05 (dd, 1H, J = J' = 4 Hz, C-6 H), 6.64 (d, 1H, J = 10 Hz, $-C\underline{H}{=}CH-CO-$), 6.15 (d, 1H, J = 10 Hz, $-CH{=}C\underline{H}-CO-$), 2.70 (s, 3H, Ar-CH_3), and 1.45 (s, 6H, 2X–CH_3); ir 1663 (C=O), 1592 (aromatic C=C), 1395, 1377, and 1364 cm^{-1} (CH_3); ms M$^+$ 186.1039 (calcd. for $C_{13}H_{14}O$: 186.1044).

4,4,7-Trimethyl-4aβ,5,8,8aβ-tetrahydro-1(4H)-naphthalenone (31)

Dienone 28 (4.89 gm, 40.0 mmol) was dissolved in anhydrous ether (100 ml) under an atmosphere of nitrogen. Boron trifluoride etherate (2.46 ml, 20.0 mmol) was added to the stirred solution and after 30 min. isoprene (12.0 ml, 120 mmol) was added. Additional portions of isoprene were added after each 24 hr. period for 6 days (12.0 ml, 120 mmol each time) and after 13 and 17 days (40.0 ml, 400 mmol each time). After 22 days the reaction mixture was cooled to 0° and a saturated aqueous solution of sodium bicarbonate (100 ml) was added dropwise. The resulting mixture was extracted with chloroform. The extracts were washed with water, dried (sodium sulfate), filtered and concentrated. Column chromatography of the residue on silica gel, eluting with 5-8% ether in Skelly B, gave a mixture of enone 31 and polymeric material. Molecular distillation in a Kugelrohr apparatus at 90° (oven temperature)/0.5 Torr gave pure enone 31 (4.62 g, 61% yield) as a colourless oil: nmr δ6.28 (dd, 1H, J = 10 Hz, J' = 1 Hz, $-\underline{\mathrm{CH}}=\mathrm{CH}-\mathrm{CO}-$), 5.68 (d, 1H, J = 10 Hz, $-\mathrm{CH}=\underline{\mathrm{CH}}-\mathrm{CO}-$), 5.18 (br.s, 1H, $-\mathrm{CH}=$), 2.89 (m, 1H, $-\overset{|}{\mathrm{C}}\mathrm{H}-\mathrm{CO}-$), 2.64 (dm, 1H, J = 14 Hz, C-8 Hb), 1.95 (br.s, 3H, C-4a H and C-5 $-CH_2-$), 1.87 (dm, 1H, J = ∼14 Hz, C-8 Ha), 1.66 (s, 3H, $=\overset{|}{\mathrm{C}}-\mathrm{CH_3}$), 1.30 (s, 3H, CH_3), and 1.09 (s, 3H, CH_3); ir (neat) 3010 (C=CH), 1675 (C=O), 1378, 1365 (CH_3), and

827 cm^{-1} (C═CH); ms M^{+} 190.1354 (calcd. for $C_{13}H_{18}O$: 190.1358). Anal. for $C_{13}H_{18}O$: C 82.06, H 9.54; Found: C 81.81, H 9.56.

4,4,7-Trimethyl-4aβ,5,8,8aα-tetrahydro-1(4H)-naphthalenone (36)

Enone 31 (459 mg, 2.42 mmol) was dissolved in methanol (20 ml) and an aqueous 1.0 N solution of sodium hydroxide (10 ml) was added. The mixture was stirred for 1 hr. The reaction mixture was then extracted with methylene chloride and the extracts were washed with water, dried, filtered and concentrated. Column chromatography of the residue on silica gel, eluting with 3% ether in petroleum ether, gave a mixture of enones 31 and 36 (400 mg, 87% yield) in a ratio of 30:70 determined by gc analysis (column A). The mixture of enones crystallized on standing and one recrystallization from ether gave white crystals of pure *trans*-enone 36 (120 mg): mp 56-60°C; nmr δ6.55 (d, 1H, J = 10 Hz, $-C\underline{H}{=}CH{-}CO-$), 5.69 (d, 1H, J = 10 Hz, $-CH{=}C\underline{H}{-}CO-$), 5.31 (m, 1H, $=CH-$), 1.67 (br.s, 3H, $=\overset{|}{C}-CH_3$), 1.13 (s, 3H, CH_3), and 1.03 (s, 3H, CH_3); ir 1673 (C═O), 1390, 1383 (CH_3), and 790 cm^{-1} (C═CH); ms M^{+} 190.1359 (calcd. for $C_{13}H_{18}O$: 190.1358). Anal. Calcd. for $C_{13}H_{18}O$: C 82.06, H 9.54; Found: C 81.94, H 9.78.

4,4,7-Trimethyl-1(4H)-naphthalenone (41)

A 40:60 mixture of *cis*- and *trans*-enones 31 and 36 (292 mg, 1.49 mmol) was dissolved in carbon tetrachloride (20 ml). *N*-Bromosuccinimide (730 mg, 2.98 mmol) and benzoyl peroxide (10 mg, 0.04 mmol) were added.

The mixture was heated at reflux with stirring for 45 min., then cooled to room temperature, filtered and concentrated. Column chromatography of the residue on silica gel, eluting with 5-7% ether in petroleum ether, gave an impure sample of aryl ketone 41. A second chromatographic purification of this material provided a pure sample of ketone 41 (106 mg, 38% yield): nmr δ7.90 (m, 1H, J = ~1 Hz, C-8 H), 7.37 (d, 1H, J = 8 Hz, C-5 H), 7.27 (dm, 1H, J = 8 Hz, J' = ~1 Hz, C-6 H), 6.78 (d, 1H, J = 10 Hz, $-\mathrm{C\underline{H}{=}CH{-}CO}-$), 6.25 (d, 1H, J = 10 Hz, $-\mathrm{CH{=}C\underline{H}{-}CO}-$), 2.43 (s, 3H, Ar-$CH_3$), and 1.47 (s, 6H, 2X-$CH_3$); ir (neat) 1665 (C=O), 1618, 1500 (aromatic C=C), 1383, 1374, 1364 (CH_3), 891, and 828 cm^{-1} (aromatic CH); ms M^+ 186.1053 (calcd. for $C_{13}H_{14}O$: 186.1044).

4,4,7-Trimethyl-3,4,4aβ,5,8,8aβ-hexahydro-1(2H)-naphthalenone (26)

Pieces of lithium ribbon (480 mg, 69 g-atom) were added to liquid ammonia (360 ml, freshly distilled from sodium) at -78° under a nitrogen atmosphere. After 15 min., a solution of enone 31 (1.00 g, 5.26 mmol) in anhydrous ether (60 ml) was added dropwise over 40 min. After stirring for an additional 90 min., solid ammonium chloride was added to discharge the blue colour and the ammonia was allowed to evaporate under a stream of nitrogen. The residue was dissolved in water and extracted with chloroform. The extracts were washed with water, 5% hydrochloric acid, water and saturated aqueous sodium chloride, dried (sodium sulfate), filtered and concentrated. Column chromatography of the residue on silica gel, eluting with 5% ether in Skelly B, gave pure ketone 26 (791 mg, 78% yield) as a colourless oil: nmr δ5.19 (m, 1H, $=CH-$), 2.89 (m, 1H, $-\overset{|}{C}H-CO-$), 2.40 (dm, 1H, J = 18 Hz, C-8 Ha), 1.64 (br.s, 3H, $=\overset{|}{C}-CH_3$), 1.32 (s, 3H, $-CH_3$), and 0.97 (s, 3H, $-CH_3$); cmr δ211.1, 131.8 118.8, 46.0, 44.5, 37.8, 35.6, 33.0, 28.7, 28.0, 26.9, 24.7, 23.2; ir (neat) 3010 (C=CH), 1712 (C=O), 1390, 1379 1366 (CH_3), and 808 cm^{-1} (C CH); ms M^+ 192.1520 (calcd. for $C_{13}H_{20}O$: 192.1514). Anal. Calcd. for $C_{13}H_{20}O$: C 81.20, H 10.48; Found: C 81.44, H 10.59.

4,4,7-Trimethyl-3,4,4aβ,5,8,8aα-hexahydro-1(2*H*)-naphthalenone (52)

Ketone 26 (611 mg, 3.18 mmol) was dissolved in methanol (60 ml) under an atmosphere of nitrogen and a 1.0 N aqueous solution of sodium hydroxide (60 ml) was added. The solution was stirred for 12 hr. and extracted with methylene chloride. The extracts were washed with water, dried, filtered and concentrated. Analysis of the residue by gc (Column B) showed the presence of *cis*-ketone 26 and *trans*-ketone 52 in a ratio of ~14:86. Column chromatography of the residue on silica gel, eluting with 2-4% ether in petroleum ether, gave *trans*-ketone 52 (471 mg, 77% yield) as low-melting white crystals (mp 25-30°C). Further elution gave a 1:1 mixture of ketones 26 and 52 (25 mg, 4% yield). Further elution gave pure *cis*-ketone (64 mg, 10% yield). *trans*-Ketone 52 showed the following spectral data: nmr δ5.24 (m, 1H, $=CH-$), 1.65 (br.s, 3H, $=\overset{|}{C}-CH_3$), 1.07 (s, 3H, CH_3), and 0.99 (s, 3H, CH_3); cmr δ212.2, 132.3, 119.5, 47.2, 45.7, 41.4, 38.2, 32.5, 30.2, 29.0, 27.0, 23.3, 19.4; 300s (C=CH), 1708 (C=O), 1392, 1372 (CH_3), and

793 cm^{-1} (C=CH); ms M$^+$ 192.1517 (calcd. for $C_{13}H_{20}O$: 192.1520). Anal. Calcd. for $C_{13}H_{20}O$: C 81.20, H 10.48; Found: C 81.06, H 10.31.

4,4,7-Trimethyl-3,4-dihydro-1(2H) naphthalenone (51)

(A) From *trans*-Ketone 52

Ketone 52 (63 mg, 0.32 mmol) was dissolved in carbon tetrachloride (10 ml) and *N*-bromosuccinimide (117 mg, 0.64 mmol) was added. The mixture was heated at reflux with stirring for 1 hr. then cooled to room temperature, filtered and concentrated. Column chromatography of the residue on silica gel, eluting with 1.5% ether in petroleum ether, gave pure aryl-ketone 51 (28 mg, 45% yield) as an oil: nmr δ7.69 (s, 1H, C-8 H), 7.19 (s, 1H, Ar-H), 7.18 (s, 1H, Ar-H), 2.57 (complex, 2H, $-CH_2-CO-$), 2.32 (s, 3H, Ar-CH_3), 1.92 (complex, 2H, $-\underline{CH_2}-CH_2-CO-$), and 1.34 (s, 6H, 2X$-CH_3$); ir 1686 (C=O), 1611, 1498 (aromatic C=C), 1390, and 1366 cm^{-1} (CH_3); ms M$^+$ 188.1195 (calcd. for $C_{13}H_{16}O$: 188.1201).

(B) From *cis*-Ketone 26

Under similar conditions, oxidation of ketone 26 (99 mg, 0.52 mmol) with *N*-bromosuccinimide (148 mg, 1.04 mmol) in carbon tetrachloride (5 ml) gave aryl-ketone 51 (34 mg, 35% yield).

Ionene (50)[43]

(A) From Aryl-Ketone 51

Aryl-ketone <u>51</u> (34 mg, 0.18 mmol) was dissolved in triethylene glycol (1.80 ml) under an atmosphere of nitrogen. Hydrazine hydrochloride (199 mg, 2.89 mmol) and anhydrous hydrazine (1.15 ml, 1.16 g, 36.2 mmol) were added. The mixture was heated at 130° (bath temperature) for 3 hr. Powdered potassium hydroxide (408 mg, 12.7 mmol based on 87% potassium hydroxide) was added and the resulting mixture was heated to 190° for 1 hr. The bath temperature was increased to 230° for 2 hr. during which condensers were exchanged and rinsed to remove volatile materials. After cooling to room temperature the reaction mixture was combined with the rinsings, diluted with water and extracted with ether. The extracts were washed with 5% hydrochloric acid and water, dried, filtered and concentrated. Column chromatography of the residue on neutral alumina (Woelm II) eluting with petroleum ether, gave pure ionene (<u>50</u>) (20 mg, 64% yield) as an oil: nmr δ7.06 (d, 1H, J = 8 Hz, $-CH{=}C\underline{H}-\overset{\|}{C}-CH_3$), 6.78 (d, 1H, J = 8 Hz, $-C\underline{H}{=}CH-\overset{\|}{C}-CH_3$), 6.70 (s, 1H, $-C\underline{H}{=}\overset{|}{C}-CH_3$), 2.66 (t, 2H, J = 6 Hz, $Ar-CH_2-$), 2.21 (s, 3H, $Ar-CH_3$), 1.66 (complex, 4H, $-C\underline{H_2}-C\underline{H_2}-$), and 1.24 (s, 6H, $2X-CH_3$); ir (neat) 1885, 1745 (Ar—H), 1616, 1500 (aromatic C=C), 1386, 1365 (CH_3), 881 and 821 cm^{-1} (Ar—H); ms M^+ 174.1410 (calcd. for $C_{13}H_{18}$: 174.1408).

(B) From β-Ionone (<u>53</u>)

Cyclodehydration of β-ionone <u>53</u> (9.6 g, 50 mmol) with iodine (50 mg, 0.20 mmol) at 270° in accordance with the procedure of Bogert and Fourman[54] produced crude ionene (<u>50</u>) which was distilled over sodium (bp 117-119°C/12 Torr) to give pure ionene (<u>50</u>) (3.45 g, 40% yield) as a fragrant colourless oil: nmr δ 7.07 (d, 1H, J = 8 Hz, $-CH{=}\underline{H}\text{-}\overset{\|}{C}-CH_3$), 6.79 (d, 1H, J = 8 Hz, $-C\underline{H}{=}CH-\overset{\|}{C}-CH_3$), 6.71 (s, 1H, $CH_2-\underset{\|}{C}-C\underline{H}{=}\underset{|}{C}-CH_3$), 2.67 (t, 2H, J = 6 Hz, Ar—CH_2—), 2.22 (s, 3H, Ar—CH_3), 1.70 (m, 4H, $-C\underline{H}_2-C\underline{H}_2-$), and 1.24 (s, 6H, 2X—$CH_3$); cmr δ 142.8, 136.0, 134.6, 129.6, 126.7, 126.6, 39.5, 33.5, 31.9 (2 carbons), 30.7, 20.8, 19.8; ir (neat) 1890, 1755 (Ar—H), 1616, 1500 (aromatic, C=C), 1388, 1367 (CH_3) 883 and 821 cm^{-1} (Ar—H); ms M^+ 174.1411 (calcd. for $C_{13}H_{18}$: 174.1407).

4,4-Dimethyl-4aβ,5,7,8,9,10,10aβ,10bβ-octahydro-1(4H)-naphthalenone (32)

Dienone <u>28</u> (160 mg, 1.31 mmol) was dissolved in anhydrous ether (10 ml). Boron trifluoride etherate (93 mg, 0.66 mmol) was added with stirring followed by 1-vinylcyclohexene (<u>54</u>) (450 mg, 2.50 mmol). After 3 days a solution of 1-vinylcyclohexene <u>54</u> (450 mg, 2.50 mmol) in ether (2.0 ml) was added. The mixture was stirred for an additional 2 days and then saturated aqueous sodium bicarbonate (1 ml) was added. The mixture was extracted with methylene chloride. The extracts were washed with water, dried, filtered and concentrated. Column chromatography of the residue on silica gel, eluting with 3-5% ether in petroleum ether, gave pure enone <u>32</u> (201 mg, 67% yield) which crystallized on standing: mp 43-47°C; nmr δ6.12 (d, 1H, J = 10 Hz, $-C\underline{H}{=}CH-CO-$), 5.57 (d, 1H, J = 10 Hz, $-CH{=}C\underline{H}-CO-$), 5.08 (br.s, 1H, $=CH-$), 2.86 (m, 1H, $-\mathrm{CO}-\overset{|}{\mathrm{C}}\mathrm{H}-$), 2.50 (dddd, 1H, J = J' = J" = 12, H''' = 4 Hz, C-10 Ha), 1.28 (s, 3H, $\mathrm{CH_3}$), and 1.04 (s, 3H, $\mathrm{CH_3}$); nmr (200 MHz, $\mathrm{CDCl_3}$) δ6.23 (d, 1H, J = 10 Hz, $-\mathrm{C\underline{H}{=}CH{-}CO}-$), 5.71 (d, 1H, J = 10 Hz, $-\mathrm{CH{=}C\underline{H}{-}CO}-$), 5.21 (s, 1H, $=\mathrm{CH}-$), 3.00 (dddd, 1H, J = J' = J" - 12, J''' = 4 Hz, C-10 Ha), 1.28 (s, 3H, $\mathrm{CH_3}$), and 1.04 (s, 3H, $\mathrm{CH_3}$); ir 1686 (C=O), 1392, 1373, and 1362 cm^{-1} ($-\mathrm{CH_3}$); ms M$^+$ 230.1666 (calcd. for $\mathrm{C_{16}H_{22}O}$: 230.1670). Anal. Calcd. for $\mathrm{C_{16}H_{22}O}$: C 83.43, H 9.63; Found: C 83.38, H 9.62.

4,4-Dimethyl-4aβ,5,7,8,9,10,10aβ,10bα-octahydro-1(4H)-phenanthrenone (37) and 3β-Methoxy-4,4-dimethyl-3,4,4aβ,5,7,8,9,10,10aβ,10bα-tetrahydro-1(2H)-phenanthrenone (55)

Enone 32 (194 mg, 0.843 mmol) was dissolved in methanol (10 ml) and a 1.0 N aqueous solution of sodium hydroxide (2.0 ml) was added. The mixture was stirred for 24 hr and then extracted with methylene chloride. The extracts were washed with water, dried, filtered and concentrated. Column chromatography of the residue on silica gel, eluting with 3% ether in petroleum ether, gave enone 37 (92 mg, 49% yield) which crystallized on standing. One recrystallization from petroleum ether gave white crystals of pure *trans*-enone 37: mp 36-45°C, nmr 6.45 (d, 1H, J = 10 Hz, $-\mathrm{C\underline{H}{=}CH{-}CO}-$), 5.68 (d, 1H, J = 10 Hz, $-\mathrm{CH{=}C\underline{H}{-}CO}-$), 5.28 (br.s, 1H, $=\mathrm{CH}-$), 1.11 (s, 3H, $-\mathrm{CH_3}$), and 1.02 (s, 3H, $-\mathrm{CH_3}$); ir 1673 (C=O), 1395, 1377, 1365 ($\mathrm{CH_3}$), and 799 cm^{-1}

(C=CH); ms M$^+$ 230.1667 (calcd. for $C_{16}H_{22}O$: 230.1670). Anal. Calcd. for $C_{16}H_{22}O$: C 83.43, H 9.63; Found: C 83.70, H 9.44. Continued elution gave a mixture (14 mg) of enone 37 and methoxy-ketone 55. Further elution with 3-5% ether in petroleum ether gave pure methoxy-ketone 55 (20 mg, 9% yield): nmr δ5.28 (br.s, 1H, =CH—), 3.27 (s, 3H, —OCH$_3$), 3.18 (dd, 1H, J = J' = 3 Hz, —O—CH—), 2.55 (d, 2H, J = 3 Hz, —CH$_2$—CO—), 1.05 (s, 3H, —CH$_3$), and 1.02 (s, 3H, —CH$_3$); ir 1712 (C=O), 1389, 1367 (CH$_3$) and 807 cm^{-1} (C=CH); ms M$^+$ 262.

4,4-Dimethyl-7,8,9,10-tetrahydro-1(4H)-phenanthrenone (42)

trans-Enone 37 (77 mg. 0.33 mmol) was dissolved in carbon tetrachloride (10 ml) and *N*-bromosuccinimide (119 mg, 0.67 mmol) and benzoyl peroxide (5 mg, 0.021 mmol) were added. The mixture was heated at reflux with stirring for 1 hr. then cooled to room temperature, filtered and concentrated. Column chromatography of the residue on silica gel, eluting with 2-3% ether in petroleum ether, gave aryl-ketone 42 (26 mg, 30% yield) which crystallized on standing. One recrystallization from petroleum ether gave yellowish crystals of aryl-ketone 42: mp 102-110°C; nmr δ7.17 (d, 1H, J = 4 Hz, C-6 H), 7.13 (d, 1H, J = 4 Hz, C-5 H), 6.59 (d, 1H, J = 10 Hz, —CH=CH—CO—), 6.12 (d, 1H, J = 10 Hz, —CH=CH—CO—), 3.24 (m, 2H, C-10 —CH$_2$—), 2.76 (m, 2H, C-7 —CH$_2$—), 1.76 (m, 4H, C-8 and C-9 —CH$_2$—), and 1.42 (s, 6H, 2X—CH$_3$); ir 1657 (C=O), 1631 (C=C), 1597 (aromatic C=C), 1375 and 1360 cm^{-1} (CH$_3$); ms M$^+$ 226.1358 (calcd. for $C_{16}H_{18}O$: 226.1358).

4,4,6,8β-Tetramethyl-4aβ,5,8,8aβ-tetrahydro-1(4H)-naphthalenone (33) and 2(1,4 Dimethyl-3-butenyl)-4,5-dimethylphenol (60)

Dienone 28 (292 mg, 2.32 mmol) was dissolved in anhydrous ether (10 ml) and boron trifluoride etherate (104 mg, 1.16 mmol) was added followed by *trans*-2-methyl-1,3-pentadiene (59) (1.90 g, 23.1 mmol). After stirring for 7 days saturated aqueous sodium bicarbonate (1 ml) was added and the resulting mixture was extracted with methylene chloride. The extracts were washed with water, dried, filtered and concentrated. Column chromatography of the residue on silica gel, eluting with 2-5% ether in petroleum ether, gave a mixture (236 mg) of enone 33 and phenol 60. Further elution with 10-50% ether in petroleum ether gave recovered dienone 28 (33 mg, 12% recovery). Flash chromatography[56] of the mixture of enone 33 and phenol 60 on silica gel, eluting with 5% ethyl acetate in petroleum ether, gave pure enone 33 (84 mg, 20% yield based on consumed starting material): nmr δ6.13 (dd, 1H, J = 10, J' = 2 Hz, $-C\underline{H}{=}CH-CO-$), 5.53 (d, 1H, J = 10 Hz, $-CH{=}C\underline{H}-CO-$), 5.19 (br.s, 1H, $=CH-$), 2.77 (dd, 1H, J = 4, J' = 3 Hz, C-8a H), 2.24 (m, 1H, $-\overset{|}{C}\underline{H}-CH_3$), 1.57 (s, 3H, $=\overset{|}{C}-CH_3$), 1.33 (d, 3H, J = 7 Hz, $-\overset{|}{C}H-C\underline{H}_3$), 1.31 (s, 3H, CH_3), and 1.09 (s, 3H, CH_3); ir 1687 (C=O), 1396, 1374, 1365 (CH_3), and 815 cm^{-1} (C=CH); ms M^+ 204.1510 (calcd. for $C_{14}H_{20}O$: 204.1514). Continued elution gave a mixture (20 mg) of ketone 33 and phenol 60 (~50:50 by nmr integration). Final elution gave pure phenol 60 (53 mg, 13% yield based on consumed starting dienone 28): nmr δ6.73 (s, 1H, C-3 Ar–H), 6.38 (s, 1H, C-6 Ar–H), 5.18 (dm, 1H, J = 9, J' = 1 Hz, $=\overset{|}{C}H-$), 4.91 (br.s, 1H, –OH), 3.70 (dq, 1H, J = 9, J' = 7 Hz, $-\overset{|}{C}\underline{H}-CH_3$), 2.14 (s, 6H, 2X Ar–$CH_3$), 1.70, 1.66 (both d, 6H total, each J = 1 Hz, $=C(CH_3)_2$), and 1.24 (d, 3H, J = 7 Hz, $-\overset{|}{C}H-C\underline{H}_3$); ir 3438 (OH), 1668 (C=C), 1619, 1510 (aromatic C=C), and 1376 cm^{-1} (CH_3); ms M^+ 204.1508 (calcd. for $C_{14}H_{20}O$: 204.1514).

4,4,6,8aα-Tetramethyl-4aβ,5,8,8aα-tetrahydro-1(4H)-naphthalenone (38) and 3β-Methoxy-4,4,6,8aα-tetramethyl-3,4,4aβ,5,8,8aα-hexahydro-1(2H)-naphthalenone (61)

Enone 33 (18 mg, 0.088 mmol) was dissolved in methanol (5 ml) and aqueous 1.0 N sodium hydroxide was added. The mixture was stirred for 20 hr., then extracted with methylene chloride. The extracts were washed with water, dried, filtered and concentrated. Column chromatography of the residue on silica gel, eluting with 1% ether in petroleum ether, gave *trans*-enone 38 (8 mg, 44% yield): nmr δ6.45 (d, 1H, J = 10 Hz, $-C\underline{H}=CH-CO-$), 5.60 (d, 1H, J = 10 Hz, $-CH=C\underline{H}-CO-$), 5.13 (br.s, 1H, =CH–), 2.38 (m, 1H, $-\overset{|}{C}\underline{H}-CH_3$), 1.66 (br.s, 3H, $=\overset{|}{C}-CH_3$), and 1.07 (s, 3H, $-CH_3$); ir (neat) 1673 (C=O), 1379, and 1366 cm^{-1} (CH_3); ms M^+ 204.1505 (calcd. for $C_{14}H_{20}O$: 204.1514). Further elution with 1-2% ether gave a mixture of enone 38 and methoxy-ketone 61 (5 mg, 75:25 by nmr integration). Final elution with 2% ether in petroleum ether gave pure methoxy-ketone 61 (5 mg, 24% yield): nmr

δ5.05 (br.s, 1H, $=CH-$), 3.22 (s, 3H, $-OCH_3$), 3.16 (dd, 1H, J = 3 Hz, $-\overset{|}{C}H-O-$), 2.53 (d, 2H, J = 3 Hz, $-CH_2-CO-$), 1.61 (s, 3H, $=\overset{|}{C}-CH_3$), 1.08 (s, 3H, $-CH_3$), 1.04 (s, 3H, $-CH_3$), and 0.93 (d, 3H, J = 7 Hz, $-\overset{|}{C}H-C\underline{H}_3$); ir 1713 (C=O), 1390, 1377, 1367 (CH_3), and 799 cm^{-1} (C=CH).

4,4,6,8-Tetramethyl-1(4$\underline{H}$)-naphthalenone (43)

Enone 33 (35 mg, 0.172 mmol) was dissolved in carbon tetrachloride (5 ml) and *N*-bromosuccinimide (61 mg, 0.343 mmol) was added followed by benzoyl peroxide (3 mg, 0.012 mmol). The mixture was heated at reflux with vigorous stirring for 1 hr. then cooled to room temperature, filtered and concentrated. Column chromatography of the residue on silica gel, eluting with 1% ether in petroleum ether, gave pure arylketone 43 (6 mg, 17% yield): nmr δ7.06 (br.s, 1H, C-7 Ar–H), 6.86 (br.s, 1H, C-5 Ar–H), 6.59 (d, 1H, J = 10 Hz, $-C\underline{H}=CH-CO-$), 6.09 (d, 1H, J = 10 Hz, $-CH=C\underline{H}-CO-$), 2.64 (s, 3H, C-8 Ar–CH_3), 2.34 (s, 3H, C-6 Ar–CH_3), and 1.43 (s, 6H, 2X–CH_3); ir 1665 (C=O), 1604 (aromatic C=C), 1395, 1375, and 1363 cm^{-1} (CH_3); ms M$^+$ 200.1199 (calcd. for $C_{14}H_{16}O$: 200.1201).

6-Carbomethoxy-4,4-dimethyl-2-cyclohexen-1-one (65)

Sodium hydride (50% oil dispersion, 15.65 g, 0.326 mol) was suspended in 1,2-dimethoxyethane (130 ml, freshly distilled over lithium aluminum hydride) under an atmosphere of nitrogen and dimethyl carbonate (73.4 g, 0.815 mol) was added. The suspension was brought to reflux while stirring with a mechanical stirrer. A solution of enone 23 (20.00 g, 0.163 mol) in dry 1,2-dimethoxyethane (60 ml) was added dropwise over 1 hr. Heating was continued for 4 hr. and then the mixture was cooled to 0°. An aqueous 10% solution of acetic acid (200 ml) was added dropwise with stirring and the mixture was extracted with ether. The extracts were washed with water, saturated aqueous sodium bicarbonate, water, and saturated aqueous sodium chloride, dried, filtered and concentrated. Column chromatography* of the residue on silica gel, eluting with 8-20% ether in Skelly B, gave keto-ester 65 (18.13 g, 61% yield) as a yellow oil. The keto-ester 65 so obtained existed partially (~40% by nmr integration) in the enol-form 65a. The following nmr data were attributed to the keto-form 65: δ6.58 (dd, 3/5H, J = 10, J' = 2 Hz, $-\underline{CH}=CH-CO-$), 5.76 (d, 3/5H, J = 10 Hz, $-CH=\underline{CH}-CO-$), 3.68 (s, 3X 3/5H, $-O-CH_3$), 3.41 (dd, 3/5H, J = 13, J' = 5 Hz, $-\overset{|}{C}H-CO_2-$), 2.25 (dd, 3/5H, J = J' = 13 Hz, $-\overset{|}{C}H-\underline{Ha}$), 1.91 (ddd, 3/5H, J = 13, J' = 5, J" = 2 Hz, $-\overset{|}{C}H-Hb$), 1.20 (s, 3X 3/5H, $-CH_3$), and 1.06 (s, 3X 3/5H, $-CH_3$). The following nmr data were attributed to the enol-form 65a: δ11.75 (s, 2/5H, $=\overset{|}{C}-OH$), 6.00 (D, 2/5H, J = 10 Hz, $=\underline{CH}-\overset{|}{C}(CH_3)_2$), 5.76 (d, 2/5H, J = 10 Hz, $=\overset{|}{C}-CH=$), 3.72 (s, 3X 2/5H, $-OCH_3$), 2.31 (s, 2X 2/5H, $-CH_2-$), 1.20 (s, 6X 2/5H, $-CH_3$). The following spectral data were recorded for the mixture of keto and enol forms 65 and 65a: ir (neat) 1744 (ester C=O),

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*Molecular distillation of the residue in a Kugelrohr apparatus (50-80° at 0.5 Torr) gave pure keto-ester 72 more conveniently but in the somewhat lower yield of 48%.[72]

1680 (enone C=O), 1658 (C=C), and 1379 cm^{-1} (CH_3); ms M^+ 182.0936 (calcd. for $C_{10}H_{14}O_3$: 182.0943). Anal. Calcd. for $C_{10}H_{14}O_3$: C 65.92, H 7.74; Found: C 66.13, H 7.74.

2 Carbomethoxy-4,4-dimethyl-2,5-cyclohexadien-1-one (64)

Keto-ester 65 (22.04 g, 0.121 mol) was dissolved in 2.204 l of a 5% solution of glacial acetic acid in *t*-butanol under an atmosphere of nitrogen. Finely divided selenium dioxide (40.25 g, 0.363 mol) was added and the mixture was stirred with a mechanical stirrer and heated to reflux. After heating for 18 hr. the mixture was cooled to room temperature, filtered and concentrated. The residue was dissolved in ether, washed with water, saturated aqueous sodium bicarbonate and water, dried, filtered and concentrated*. Column chromatography of the residue on silica gel, eluting with 25-30% ether in Skelly B, gave *t*-butyl-ester 67 (2.18 g, 8% yield) as a crystalline solid. Two recrystallizations from ether gave pinkish-white** crystals of *t*-butyl ester 66: mp 117-120°C; nmr δ7.15 (d, 1H, J = 3 Hz, $-CH{=}\overset{|}{C}-CO_2-$), 6.68 (dd, 1H, J = 10, J' = 3 Hz, $-C\underline{H}{=}CH-CO-$), 6.11 (d, 1H, J = 10 Hz, $-CH{=}C\underline{H}-CO-$), 1.59 (s, 9H, $-OC(CH_3)_3$), and 1.39 (s, 6H, 2X$-CH_3$); ir 1723 (ester C=O), 1652 (ketone C=O), 1390 and 1367 cm^{-1} (CH_3); ms M^+ 222.1259 (calcd. for $C_{13}H_{18}O_3$: 222.1256). Anal. Calcd. for $C_{13}H_{18}O_3$:

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*Brief heating of the residue in refluxing dimethylformamide[73] did not completely remove red selenium.

**The pinkish colour is probably due to contamination by red selenium.

C 70.24, H 8.16; Found: C 70.01, H 8.10. Further elution with 50-100% ether in petroleum ether gave keto-ester 64 which was contaminated with red selenium. Molecular distillation of this material in a Kugelrohr apparatus (120°C/0.5 Torr) gave pure keto-ester 64 (17.4 g, 80% yield*) as a yellow oil: nmr δ7.33 (d, 1H, J = 3 Hz, $-C\underline{H}{=}\overset{|}{C}-CO_2-$), 6.80 (dd, 1H, J = 10, J' = 3 Hz, $-C\underline{H}{=}CH-CO-$), 6.06 (d, 1H, J = 10 Hz, $-\overset{|}{C}H{=}C\underline{H}-CO-$), 3.74 (s, 3H, $-OCH_3$), and 1.33 (s, 6H, $2X-CH_3$); ir (neat) 1734 (ester C=O), 1660 (ketone C=O), 1398, 1384 and 1360 cm^{-1} (CH_3); ms M^+ 180.07834 (calcd. for $C_{10}H_{12}O_3$: 180.07865). Anal. Calcd. for $C_{10}H_{12}O_3$: C 66.65, H 6.71; Found C 66.33, H 6.70.

8aβ-Carbomethoxy-4,4-dimethyl-4aβ,5,8,8a-tetrahydro-1(4H)-naphthalenone (67)

Dienone-ester 64 (311 mg, 1.73 mmol) was dissolved in ether (20 ml, distilled over lithium aluminum hydride) under an atmosphere of nitrogen. Boron trifluoride etherate (106 μl, 122 mg, 0.86 mmol) was added and after stirring for 15 min. dry butadiene gas (passed through calcium sulfate) was bubbled into the solution. After 6 hr. saturated aqueous sodium bicarbonate (2 ml) was added and the resulting mixture was extracted with chloroform. The extracts were washed with water, dried, filtered and concentrated. Column chromatography of the residue on silica gel eluting with 10% ether in Skelly B

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*On one occasion after refluxing the reaction for 6.5 hr. a yield of 87% was obtained, based on consumption of 88% of the starting material.

gave pure keto-ester 67 (286 mg, 70% yield): nmr ($CDCl_3$) δ6.57 (d, 1H, J = 10 Hz, $-C\underline{H}=CH-CO-$), 5.87 (d, 1H, J = 10 Hz, $-CH=C\underline{H}-CO-$), 5.66 (m, 2H, $-CH=CH-$), 3.70 (s, 3H, $-O-CH_3$), 2.75 (dd, 1H, J = 6, J' = 4 Hz, C-4a H), 2.70 (dm, 1H, J = 18 Hz, C-8 Hb), 2.25 (dm, 1H, J = 18 Hz, C-8 Ha), 2.11 (m, 2H, C-5 $-CH_2-$), 1.18 (s, 3H, $-CH_3$), and 1.07 (s, 3H, $-CH_3$); ir (KBr disk) 1730 (ester C=O), 1663 (enone C=O), 1619 (C=C), 1384, 1373, and 1361 cm^{-1} (CH_3); ms M^+ 234.1258 (Calcd. for $C_{14}H_{18}O_3$: 234.1256). Anal. Calcd. for $C_{14}H_{18}O_3$: C 71.77, H 7.74; Found: C 72.01, H 7.80.

8aβ-Carbomethoxy-4,4,6,7-tetramethyl-4aβ,5,8,8a-tetrahydro-1(4H)-naphthalenone (68)

Dienone-ester 64 (343 mg, 1.91 mmol) was dissolved in ether (20 ml, distilled over lithium aluminum hydride) under an atmosphere of nitrogen. Boron trifluoride etherate (118 μl, 136 mg, 0.96 mmol) was added and, after 15 min., 2,3-dimethyl-1,3-butadiene (4.34 ml, 3.15 g, 38.2 mmol) was added. After stirring for 4 days saturated aqueous sodium bicarbonate (3 ml) was added and the resulting mixture was extracted with methylene chloride. The extracts were washed with water, dried, filtered and concentrated. Column chromatography of the residue on silica gel, eluting with 10% ether in Skelly B, gave pure keto-ester 68 (316 mg, 63% yield). An analytical sample was prepared by molecular distillation in a Kugelrohr apparatus (60°C at 1 Torr) and this sample crystallized on standing: mp 77.5-78.5°C;

nmr δ6.46 (d, 1H, J = 10 Hz, $-C\underline{H}=CH-CO-$), 5.75 (d, 1H, J = 10 Hz, $-CH=C\underline{H}-CO-$), 3.61 (s, 3H, $-O-CH_3$), 2.63 (dd, 1H, J = 6, H' = 4 Hz, C-4a H), 2.47 (d, 1H, J = 18 Hz, C-8 Hb), 2.09 (d, 1H, J = 18 Hz, C-8 Ha), 1.92 (br.s, 2H, C-5 $-CH_2-$), 1.58 (s, 6H, 2X $-C=\overset{|}{C}-CH_3$), 1.13 (s, 3H, $-CH_3$), and 0.94 (s, 3H, $-CH_3$); ir (neat) 1746 (ester C=O), 1676 (enone C=O), 1383 and 1370 cm^{-1} (CH_3); ms M^+ 262.1568 (calcd. for $C_{16}H_{22}O_3$: 262.1569). Anal. Calcd. for $C_{16}H_{22}O_3$: C 73.25, H 8.45; Found: C 73.06, H 8.51.

8aβ-Carbomethoxy-4,4-dimethyl-5,8β-methano-4aβ,5,8,8a-tetrahydro-1(4H)-naphthalenone (69)

Dienone-ester 64 (297 mg, 1.65 mmol) was dissolved in ether (20 ml, distilled over lithium aluminum hydride) under an atmosphere of nitrogen. Boron trifluoride etherate (100 μl, 116 mg, 0.82 mmol) was added and after stirring for 20 min. a solution of cyclopentadiene* (2.71 ml, 2.17 g, 33 mmol) in dry ether (5 ml) was added. After stirring for 3 hr. saturated aqueous sodium bicarbonate (2 ml) was added and the resulting mixture was extracted with methylene chloride. The extracts were washed with water, dried, filtered and concentrated. Column chromatography of the residue on silica gel, eluting with 10% ether in Skelly B, gave pure keto-ester 69 (284 mg, 70% yield) which

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*Cyclopentadiene was prepared by thermal cracking of dicyclopentadiene and was stored at -30° prior to use.

crystallized on standing. An analytical sample was prepared by molecular distillation in a Kugelrohr apparatus (60° at 10 Torr): mp 57-59°C; nmr δ6.31 (dd, 1H, J = 10, J' = 1.5 Hz, $-C\underline{H}=CH-CO-$), 6.05, 5.75 (each dd, each 1H, each J = 6, J' = 2.5 Hz, $-CH=CH-$), 5.60 (d, 1H, J = 10 Hz, $-CH=C\underline{H}-CO-$), 3.65 (s, 3H, $-O-CH_3$), 3.45 (m, 1H, C-8 H), 3.00 (m, 1H, C-5 H), 2.49 (dd, 1H, J = 2.5, J' = 1.5 Hz, C-4a H), 1.60 (d, 1H, J = 9 Hz, bridge $-CH\underline{H}-$), 1.41 (ddd, 1H, J = 9, J' = J" = 2 Hz, bridge $-CH\underline{H}-$), 1.27 (s, 3H, $-CH_3$), and 1.17 (s, 3H, $-CH_3$); ir (neat) 1738 (ester C=O), 1662 (enone C=O), 1379, 1366 (CH_3), and 720 cm^{-1} (C=CH); ms M^+ 246.1253 (calcd. for $C_{15}H_{18}O_3$: 246.1256). *Anal.* Calcd. for $C_{15}H_{18}O_3$: C 73.15, H 7.37; Found C 72.88, H 7.42.

8aβ-Carbomethoxy-4,4,8α-trimethyl-4aβ,5,8,8a-tetrahydro-1(4*H*)-naphthalenone (70) and 2-Carbomethoxy-4,4,8α-trimethyl-4aβ,5,8,8aβ-tetrahydro-1(4*H*)-naphthalenone (81)

Dienone-ester 64 (287 mg, 1.59 mmol) was dissolved in ether (20 ml) under an atmosphere of nitrogen. Boron trifluoride etherate (98 μl, 114 mg, 0.80 mmol) was added and after 15 min., *trans*-piperylene (1.59 ml, 15.9 mmol) was added. After stirring for 43 hr. saturated aqueous sodium bicarbonate (2 ml) was added and the resulting mixture was extracted with methylene chloride. The extracts were washed with water, dried, filtered and concentrated. Column chromatography of the residue on silica gel, eluting with 7-8% ether in petroleum ether, gave keto-ester 70 (329 mg, 83% yield) which crystallized on standing. One recrystallization from ether gave white crystals of pure keto-ester 70: mp 66-68°C; nmr δ6.11 (dd, 1H, J = 10, J' = 2 Hz, $-C\underline{H}=CH-CO-$), 5.72 (d, 1H, J = 10 Hz, $-CH=C\underline{H}-CO-$), 5.50, 5.35 (each dm, 2H, each J = 12 Hz, $-CH=CH-$), 3.67 (s, 3H, $-O-CH_3$), 2.70 (m, 1H, $-\overset{|}{C}\underline{H}-CH_3$), 2.56 (ddd, 1H, J = 11, J' = 6, J" = 2 Hz, C-4a H), 2.10 (m, 2H, C-5 $-CH_2-$), 1.20 (d, 3H, J = 8 Hz, $-\overset{|}{C}H-C\underline{H_3}$), 1.14 (s, 3H, $-CH_3$), and 1.10 (s, 3H, $-CH_3$); ir (neat) 3010 (HC=CH), 1725 (ester C=O), 1685 (enone C=O), and 1375 cm^{-1} (CH_3); ms M$^+$ 248.1413 (Calcd. for $C_{15}H_{20}O$: 248.1414). Anal. Calcd. for $C_{15}H_{20}O$: C 72.55, H 8.12; Found: C 72.52, H 8.13. Further elution with 8-20% ether in petroleum ether gave keto-ester 81 (22 mg, 6% yield): nmr δ6.78 (d, 1H, J = 2 Hz, $-CH=\overset{|}{C}-CO-$), 5.45 (complex, 2H, $-HC=CH-$), 3.73 (s, 3H, $-O-CH_3$), 2.96 (dd, 1H, J + J' = 4 Hz, $-CO-\overset{|}{C}H-$), 2.33 (m, 1H, $-\overset{|}{C}\underline{H}-CH_3$), 1.39 (s, 3H, $-CH_3$), 1.36 (d, 3H, J = 8 Hz, $-\overset{|}{C}H-C\underline{H_3}$), and 1.18 (s, 3H, $-CH_3$); ms M$^+$ 248.

Lithium Iodide Dihydrate-Collidine Reagent

Finely divided anhydrous lithium iodide (514 mg, 3.84 mmol) was suspended in 2,4,6-collidine (3.05 ml) with vigorous stirring. Water (138 μl, 138 mg, 7.68 mmol) was added and the suspension rapidly dissolved. The resulting pale yellow solution had a calculated concentration of 1.28 N in lithium iodide dihydrate.

4,4,8α-Trimethyl-4aβ,5,8α,8aβ-tetrahydro-1(4H)-naphthalenone (30) from Keto-ester 70

Keto-ester 70 (315 mg, 1.27 mmol) was dissolved in lithium iodide dihydrate-collidine reagent (2.04 ml, 2.61 mmol) and heated at reflux with stirring. After 1 hr. the mixture was cooled to room temperature, poured into cold 5% aqueous hydrochloric acid and extracted with ether. The extracts were washed with 5% aqueous hydrochloric acid and water, dried, filtered and concentrated. Column chromatography of the residue on silica gel eluting with 2% ether in petroleum ether gave pure *cis*-enone 30 (104 mg, 45% yield based on consumed starting material) which was identical in its nmr and ir spectra with *cis*-enone 30 previously reported (*vide supra*). Further elution with 4-10% ether in petroleum ether gave keto-ester 70 (86 mg, 27% recovery).

8aβ-Carbomethoxy-4,4,8β-trimethyl-4aβ,5,8,8a-tetrahydro-1(4H)-naphthalenone (71) and 8aβ-Carbomethoxy-4,4,8α-trimethyl-4aβ,5,8,8a-tetrahydro-1(4H)-naphthalenone (70)

Dienone ester 64 (360 mg, 2.0 mmol) was dissolved in anhydrous ether (10 ml) and ferric chloride (162 mg, 1.0 mmol) was added followed quickly by *cis*-piperyline* (1.97 ml, 1.36 g, 20 mmol). After stirring for 90 min. saturated aqueous sodium bicarbonate (2 ml) was added and the resulting mixture was extracted with methylene chloride. The

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extracts were washed with water, dried, filtered and concentrated. Column chromatography of the residue on silica gel, eluting with 10-20% ether in petroleum ether, gave a mixture of keto-esters <u>70</u> and <u>71</u> (223 mg, 45% yield, 74% based on consumption of 61% of the starting dienone-ester <u>64</u>, 50:50 mixture by nmr integration). One recrystallization from ether gave white crystals of keto-ester <u>71</u> (58 mg): mp 110-132°C; nmr δ6.40 (d, 1H, J = 10 Hz, $-C\underline{H}{=}CH-CO-$), 5.74 (d, 1H, J = 10 Hz, $-CH{=}C\underline{H}-CO-$), 5.48 (s, 1H, $=CH-$), 3.60 (s, 3H, $-O-CH_3$), 2.63 (dd, 1H, J = J' = 5 Hz, C-4a H), 2.52 (dq, 1H, J = 7, J' = 4 Hz, $-C\underline{H}-CH_3$), 2.02 (m, 2H, C-5 $-CH_2-$), 1.18 (s, 3H, $-CH_3$), 1.10 (d, 3H, J = 7 Hz, $-CH-C\underline{H}_3$), and 1.06 (s, 3H, $-CH_3$); ir 1741 (ester C═O), 1668 (enone C═O), 1382, 1376 (CH_3), and 702 cm^{-1} (HC═CH); ms M^+ 248.1414 (calcd. for $C_{15}H_{20}O_3$: 248.1412). <u>Anal.</u> Calcd. for $C_{15}H_{20}O_3$: C 72.55, H 8.21; Found: C 72.65, H 8.02. One recrystallization of the mother liquor gave additional colourless crystals of keto-ester <u>71</u> (37 mg). Further elution with ether gave dienone-ester <u>64</u> (142 mg, 39% recovery).

<u>4,4,8β-Trimethyl-4aβ,5,8,8aβ-tetrahydro-1(4H)-naphthalenone (47) and 4,4,8β-Trimethyl-4aβ,5,8,8aα-tetrahydro-1(4H)-naphthalenone (77)</u>

Keto-ester <u>71</u> (67 mg, 0.27 mmol) was dissolved in 2,4,6-collidine (2 ml) under an argon atmosphere. Anhydrous lithium iodide (224 mg, 1.67 mmol) was added followed by water (58 μl, 58 mg, 3.24 mmol). The mixture was heated at reflux with vigorous stirring for 90 min. then cooled to room temperature, poured into cold aqueous 5% hydrochloric acid and extracted with ether. The extracts were washed with aqueous 5% hydrochloric acid and water, dried, filtered and concentrated. Column chromatography of the residue on silica gel, eluting with 3-5% ether in petroleum ether, gave a 32:68 mixture of *cis*- and *trans*-enones 47 and 77 (33 mg, 64% yield). The nmr spectrum showed two sets of signals; one assignable to *cis*-ketone 47: δ6.27 (dd, 1/3H, J = 10, J' = 2 Hz, $-C\underline{H}=CH-CO-$), 5.70 (d, 1/3H, J = 10 Hz, $-CH=C\underline{H}-CO-$), 5.70-5.40 (complex, 2X 1/3H, $-HC=CH-$), 3.06 (m, 1/3H, $-C\underline{H}-CH_3$), 2.55 (m, 1/3H, $-CH-CO-$), 1.30 (s, 3X 1/3H, $-CH_3$), 1.12 (s, 3X 1/3 H, $-CH_3$), and 1.04 (d, 3X 1/3H, J = 7 Hz, $-CH-C\underline{H}_3$); the other assignable to the *trans*-enone 77: δ6.60 (d, 2/3H, J = 10 Hz, $-C\underline{H}=CH-CO-$), 5.77 (d, 2/3H, J = 10 Hz, $-CH=C\underline{H}-CO-$), 5.70-5.40 (complex, 2X 2/3H, $-HC=CH-$), 2.83 (ddq, 2/3H, J = 7, J' = J" ~ 5 Hz, $-C\underline{H}-CH_3$), 1.17 (s, 3X 2/3H, CH_3), 1.04 (s, 3X 2/3H, CH_3). The following data were recorded on the mixture of 47 and 77: ir 1671, 1655 (C=O), 1396, 1378, 1367 (CH_3), and 714 cm^{-1} (HC=CH); ms M^+ 190.1356 (calcd. for $C_{13}H_{18}O$: 190.1357).

4,4,8-Trimethyl-1(4H)-naphthalenone (40)

A mixture of *cis*- and *trans*-enones 47 and 77 (32:68, 24 mg, 0.13 mmol) was dissolved in carbon tetrachloride (5 ml) and *N*-bromosuccinimide (45 mg, 0.25 mmol) and benzoyl peroxide (2 mg, 0.008 mmol) were added. The mixture was heated at reflux for 1 hr. then cooled to room temperature, filtered, and concentrated. Column chromatography of the residue on silica gel, eluting with 0.5% ether in petroleum ether, gave aryl-ketone 40 (9 mg, 38% yield).

8aβ-Carbomethoxy-4,4,6-trimethyl-4aβ,5,8,8aβ-tetrahydro-1(4H)-naphthalenone (72) and 8aβ-Carbomethoxy-4,4,7-trimethyl-4aβ,5,8,8aβ-tetrahydro-1(4H)-naphthalenone (73)

Dienone-ester 64 (517 mg, 2.87 mmol) was dissolved in ether (10 ml, distilled over lithium aluminum hydride) under an atmosphere of nitrogen. Boron trifluoride etherate (177 μl, 205 mg, 1.44 mmol) was added and after 15 min. a solution of isoprene (5.74 ml, 57.4 mmol) in dry ether (10 ml) was added. After stirring for 3 days saturated aqueous sodium bicarbonate (10 ml) was added and the resulting mixture was extracted with ether. The extracts were washed with water, dried, filtered and concentrated. Column chromatography of the residue on silica gel, eluting with 10-12% ether in Skelly B, gave a 70:30 mixture (by gc analysis on Column A) of keto-esters 72 and 73 (525 mg, 73% yield). A 1.70 g sample of a similar mixture was separated by preparative high pressure liquid chromatography on a Waters Associates Prep LC/System 500 using one silica gel cartridge and eluting with 50% ether in petroleum ether. Fractions were collected by shaving the leading and trailing edges of the single peak and recycling the central portion. The combined "leading edge" fractions were concentrated to give a sample which was shown by gc analysis (Column A) to be predominantly keto-ester 72 (445 mg, lower gc retention time isomer). This sample crystallized on standing and two recrystallizations from ether gave colourless rhombs of pure keto-ester 72:

mp 95-113°C; nmr δ6.43 (d, 1H, J = 10 Hz, $-C\underline{H}{=}CH{-}CO-$), 5.76 (d, 1H, J = 10 Hz, $-CH{=}C\underline{H}{-}CO-$), 5.29 (m, 1H, $=CH-$), 3.64 (s, 3H, $-O-CH_3$), 2.62 (ddd, 1H, J = 5, J' = 4, J" = 0.5 Hz, C-4a H), 2.47 (br.d, 1H, J = 17 Hz, C-8 Hb), 2.08 (br.d, 1H, J = 17 Hz, C-8 Ha), 2.01 (m, 2H, C-5 $-CH_2-$), 1.66 (br.s, 3H, $=\overset{|}{C}-CH_3$), 1.16 (s, 3H, $-CH_3$), and 1.00 (s, 3H, $-CH_3$); ir (neat) 1744, 1730 (ester C=O), 1672 (enone (C=O), 1384 and 1371 cm^{-1} (CH_3); ms M$^+$ 248.1410 (calcd. for $C_{15}H_{20}O$: 248.1413). Anal. Calcd. for $C_{15}H_{20}O$: C 72.55, H 8.12; Found: C 72.41, H 8.08. The "trailing edge" fractions were combined and concentrated to give a sample which was shown by gc analysis (Column A) to be predominantly keto-ester 73 (161 mg, higher gc retention time isomer). This sample crystallized on standing and two recrystallizations from ether gave colourless rhombs of pure keto-ester 73: mp 91.5-92.5°C; nmr δ6.41 (d, 1H, J = 10 Hz, $-C\underline{H}{=}CH{-}CO-$), 5.75 (d, 1H, J = 10 Hz, $-CH{=}C\underline{H}{-}CO-$), 5.34 (br.s, 1H, $=CH-$), 3.67 (s, 3H, $-O-CH_3$), 2.71 (dd, 1H, J = 6, J' = 3 Hz, C-4a H), 2.62 (dm, 1H, J = 19 Hz, C-8 Hb), 2.14 (dm, 1H, J = 19 Hz, C-8 Ha), 1.91 (m, 2H, C-5 $-CH_2-$), 1.67 (br.s, 3H, $=\overset{|}{C}-CH_3$), 1.19 (s, 3H, $-CH_3$), and 1.02 (s, 3H, $-CH_3$); ir 1740 (ester C=O), 1667 (enone C=O), 1376 (CH_3), and 828 cm^{-1} (C=CH); ms M$^+$ 248.1412 (calcd. for $C_{15}H_{20}O_3$: 248.1412). Anal. Calcd. for $C_{15}H_{20}O_3$: C 72.55, H 8.21; Found: C 72.71, H 8.29. A total of 1.09 g of a mixture of keto-esters 72 and 73 was also recovered from the preparative liquid chromatography.

4,4,7-Trimethyl-4aβ,5,8,8aβ-tetrahydro-1(4H)-naphthalenone (31) and 4,4,7-Trimethyl-4aβ,5,8,8aα-tetrahydro-1(4H)-naphthalenone (36) from Keto-ester 72

Keto-ester 72 (336 mg, 1.35 mmol) was dissolved in lithium iodide dihydrate-collidine reagent (2.12 ml, 2.70 mmol) under an atmosphere of nitrogen. The mixture was stirred vigorously and heated at reflux for 3 hr. The mixture was then cooled to room temperature, poured into cold aqueous 5% hydrochloric acid and extracted with ether. The extracts were washed with cold 5% aqueous hydrochloric acid and water, dried, filtered and concentrated. Column chromatography of the residue on silica gel, eluting with 4-8% ether in petroleum ether, gave a mixture of *cis*- and *trans*-enones 31 and 36 (50:50 by nmr integration, 195 mg, 76% yield, 97% based on consumed starting material). Further elution with 8-25% ether in petroleum ether gave recovered keto-ester 72 (75 mg, 22% recovery). The nmr spectrum of the product mixture showed two sets of signals identical to those already reported (*vide supra*) for pure *cis*-enone 31 and pure *trans*-enone 36.

4,4,7-Trimethyl-1(4H)-naphthalenone (41) (via keto-ester 72)

The mixture of *cis*- and *trans*-enones 31 and 36 (50:50 by nmr integration, 120 mg, 0.645 mmol) obtained by decarboxylation of keto-ester 72 (*vide supra*) was dissolved in carbon tetrachloride (10 ml).

N-Bromosuccinimide (230 mg, 1.29 mmol) and benzoyl peroxide (5 mg, 0.021 mmol) were added. The mixture was heated with stirring for 1 hr. then cooled to room temperature, filtered and concentrated. Column chromatography of the residue on silica gel, eluting with 1-2% ether in petroleum ether, gave an impure sample of aryl-ketone 41 which was subjected to a second chromatographic purification. This provided fairly pure aryl-ketone 41 (44 mg, 37% yield), the nmr spectrum of which was identical to that already reported (*vide supra*).

4,4,6-Trimethyl-4aβ,5,8,8aβ-tetrahydro-1(4H) naphthalenone (48) and 4,4,6-Trimethyl-4aβ,5,8,8aα-tetrahydro-1(4H) naphthalenone (78)

Keto-ester 73 (248 mg, 1.00 mmol) was dissolved in the lithium iodide dihydrate-collidine reagent (2.34 ml, 3.00 mmol) and the mixture was brought to reflux. After heating for 3 hr. the mixture was cooled to room temperature, poured into cold aqueous 5% hydrochloric acid and extracted with ether. The extracts were washed with cold 5% aqueous hydrochloric acid and water, dried, filtered and concentrated. Column chromatography of the residue on silica gel, eluting with 4-10% ether in petroleum ether, gave a mixture of *cis*- and *trans*-enones 48 and 78 (43:57 by nmr integration, 174 mg, 91% yield, 97% based on consumed starting material). Further elution with 10-15% ether in petroleum ether gave keto-ester 73 (18 mg, 7% recovery). The nmr spectrum of the product mixture exhibited two sets of signals.

The following nmr data were attributed to the *cis*-enone 48: δ6.29 (dd, $\sim$2/5H, J = 10, J' = 2 Hz, $-C\underline{H}{=}CH{-}CO{-}$), 5.68 (d, $\sim$2/5H, J = 10 Hz, $-CH{=}C\underline{H}{-}CO{-}$), 5.33 (m, $\sim$2/5H, $=CH-$), 2.82 (m, $\sim$2/5H, $-CO-\overset{|}{C}H-$), 1.58 (br.s, 3X $\sim$2/5H, $=\overset{|}{C}-CH_3$), 1.30 (s, 3X $\sim$2/5 H, $-CH_3$), and 1.10 (s, 3X $\sim$2/5H, $-CH_3$). The following nmr data were attributed to the *trans*-enone 78: δ6.56 (d, $\sim$3/5H, J = 10 Hz, $-C\underline{H}{=}CH{-}CO{-}$), 5.72 (d, $\sim$3/5H, J = 10 Hz, $-CH{=}C\underline{H}{-}CO{-}$), 5.33 (m, $\sim$3/5H, $=CH-$), 1.66 (br.s, 3X $\sim$3/5H, $=\overset{|}{C}-CH_3$), 1.14 (s, 3X $\sim$3/5H, $-CH_3$), and 1.04 (s, 3X $\sim$3/5H, $-CH_3$). The following spectral data were recorded for the mixture of *cis*- and *trans*-enones 48 and 78: ir (CCl_4): 1686 (C=O), 1675 (C=O), 1397, 1379, 1367 (CH_3), 790 cm^{-1} (C=CH): ms M^+ 190.1352 (calcd. for $C_{13}H_{18}O$: 190.1357). Anal. Calcd. for $C_{13}H_{18}O$: C 82.06, H 9.54; Found C 82.06, H 9.55.

4,4,6-Trimethyl-1(4H)-naphthalenone (49)

A mixture of *cis*- and *trans*-enones 48 and 78 (43:57 by nmr integration, 58 mg, 0.31 mmol) was dissolved in carbon tetrachloride (10 ml) and *N*-bromosuccinimide (109 mg, 0.61 mmol) and benzoyl peroxide (5 mg, 0.02 mmol) were added. The mixture was stirred vigorously and heated at reflux for 45 min., then cooled to room temperature, filtered and concentrated. Column chromatography of the residue on silica gel, eluting with 1.5-2% ether in petroleum ether, gave an impure sample of aryl-ketone 49 which was subjected to a second chromatographic purification. This provided pure aryl-ketone 49 (25 mg, 43% yield):

nmr δ7.95 (d, 1H, J = 8 Hz, C-8 H), 7.20 (br.s, 1H, C-5 H), 7.09 (dd, 1H, J = 8, J' = 2 Hz, C-7 H), 6.72 (d, 1H, J = 10 Hz, $-C\underline{H}{=}CH{-}CO-$), 6.18 (d, 1H, J = 10 Hz, $-CH{=}C\underline{H}{-}CO-$), 2.40 (s, 3H, $Ar{-}CH_3$), and 1.44 (s, 6H, $2X{-}CH_3$); ir 1661 (C=O), 1607 (aromatic C=C), 1395, 1372, 1359 (CH_3), 814 (aromatic CH); ms M^+ 186.1047 (calcd. for $C_{13}H_{14}O$: 186.1045).

10bβ-Carbomethoxy-4,4-dimethyl-4aβ,5,7,8,9,10,10aβ,10b-octahydro-1(4H)-phenanthrenone (74)

Dienone-ester 64 (360 mg, 2.0 mmol) was dissolved in anhydrous ether (20 ml) under an atmosphere of nitrogen. Boron trifluoride etherate (126 μl, 142 mg, 1.0 mmol) was added and after 15 min. a solution of 1-vinylcyclohexene (54) (2.53 ml, 2.16 g, 20 mmol) in anhydrous ether (20 ml) was added. After stirring for 60 hr. saturated aqueous sodium bicarbonate (10 ml) was added and the resulting mixture was extracted with ether. The extracts were washed with water, dried, filtered and concentrated. Column chromatography of the residue on silica gel, eluting with 10-12% ether in petroleum ether, gave keto-ester 74 (501 mg, 87% yield) which crystallized on standing. One recrystallization from ether-petroleum ether gave white crystals of pure keto-ester 74: mp 75.5-77°C; nmr δ6.20 (d, 1H, J = 10 Hz, $-C\underline{H}{=}CH{-}CO-$), 5.76 (d, 1H, J = 10 Hz, $-CH{=}C\underline{H}{-}CO-$), 5.16 (br.s, 1H, $=CH$), 3.66 (s, 3H, $-O{-}CH_3$), 2.70 (m, 1H, C-10a H), 2.56 (dd, 1H, J = J' = 6 Hz, C-4a H), 2.28 (dm, 1H, J = 14 Hz, C-7 Hc), 2.03 (br.s, 3H, C-5 $-CH_2-$ and C-7 Hd), 1.30 (m, 4H, C-8 and C-9 $-CH_2-$), 1.16 (s, 3H, $-CH_3$), and 1.10 (s, 3H, $-CH_3$); ir 1728 (ester C=O), 1689 (enone C=O), 1370 (CH_3), and 835 cm^{-1} (C=CH); ms M^+ 288.1725 (calcd. for $C_{18}H_{24}O_3$: 288.1725). Anal. Calcd. for $C_{18}H_{24}O_3$: C 74.97, H 8.39; Found C 74.79, H 8.32.

4,4-Dimethyl 4aβ,5,7,8,9,10,10aβ,10bβ-octahydro-1(4H)-phenanthrenone (32) and 4,4-Dimethyl 4aβ,5,7,8,9,10,10aβ,10bα-octahydro-1(4H)-phenanthrenone 37) from Keto-ester 74

Keto-ester 74 (170 mg, 0.59 mmol) was dissolved in lithium iodide dihydrate-collidine reagent (1.26 ml, 1.62 mmol). The mixture was heated at reflux with stirring for 1 hr. then cooled to room temperature, poured into cold aqueous 5% hydrochloric acid and extracted with ether. The extracts were washed with cold 5% aqueous hydrochloric acid and water, dried, filtered and concentrated. Column chromatography of the residue on silica gel, eluting with 2% ether in petroleum ether, gave a mixture of *cis*- and *trans*-enones 32 and 37 (47:53 by nmr integration, 83 mg, 61% yield). The nmr spectrum of this mixture showed two sets of signals identical with those already reported for *cis*-enone 32 and *trans*-enone 37 (*vide supra*).

4,4-Dimethyl-7,8,9,10-tetrahydro-1(4H)-phenanthrenone (42) from Keto-ester 74

A mixture of *cis*- and *trans*-enones 32 and 37 (47:53 by nmr integration, 81 mg, 0.35 mmol) obtained by decarboxylation of keto-ester 74 was dissolved in carbon tetrachloride (10 ml) and *N*-bromosuccinimide (125 mg, 0.70 mmol) was added. The mixture was heated at reflux with stirring for 1 hr., then cooled to room temperature, filtered and concentrated. Column chromatography of the residue on silica gel, eluting with 1.5% ether in petroleum ether, gave aryl ketone 42 (16 mg, 20% yield) which showed an nmr spectrum identical with that already reported for aryl-ketone 42 (*vide supra*).

8aβ-Carbomethoxy-4,4,6,8α-tetramethyl-4aβ,5,8,8a-tetrahydro-1(4H)-naphthalenone (75) and 8aβ-Carbomethoxy-4,4,6,8β-tetramethyl-4aβ,5,8,8a-tetrahydro-1(4H)-naphthalenone (76)

Dienone-ester 64 (329 mg, 1.83 mmol) was dissolved in anhydrous ether (10 ml) and boron trifluoride etherate (112 μl, 130 mg, 0.95 mmol) was added. After stirring for 10 min. *trans*-2-methyl-1,3-pentadiene (59) (2.08 ml, 1.50 g, 18.3 mmol) was added. The mixture was stirred for 2 hr. and saturated aqueous sodium bicarbonate (2 ml) was added. The resulting mixture was extracted with methylene chloride and the extracts were washed with water, dried, filtered and concentrated. Column chromatography of the residue on silica gel, eluting with 5-20% ether in petroleum ether, gave a mixture of keto-esters 75 and 76 (396 mg, 83% yield, 50:50 by nmr integration). One recrystallization from ether gave white crystals of pure keto-ester 76 (72 mg): mp

112-116°C; nmr δ6.40 (d, 1H, J = 10 Hz, $-\underline{CH}{=}CH{-}CO{-}$), 5.73 (d, 1H, J = 10 Hz, $-CH{=}\underline{CH}{-}CO{-}$), 5.20 (br.s, 1H, $=CH-$), 3.60 (s, 3H, $-O-CH_3$), 2.63 (dd, 1H, J = 6, J' = 4 Hz, C-4a H), 2.52 (m, 1H, $-\underline{CH}-CH_3$), 1.89 (br.s, 2H, C-5 $-CH_2-$), 1.65 (s, 3H, $=C-CH_3$), 1.16 (s, 3H, $-CH_3$), 1.07 (d, 3H, J = 8 Hz, $-CH-C\underline{H}_3$), and 1.02 (s, 3H, $-CH_3$); ir 1739 (ester C=O), 1672 (enone C=O), 1382, 1377, and 1369 cm^{-1} (CH_3); ms M^+ 262.1574 (calcd. for $C_{16}H_{22}O_3$: 262.1569). Anal. Calcd. for $C_{16}H_{22}O_3$: C 73.25, H 8.45; Found: C 73.21, H 8.38. One recrystallization from the mother liquor gave white crystals of pure keto-ester 75 (28 mg): mp 97-104°C; nmr δ6.09 (dd, 1H, J = 10, J' = 2 Hz, $-\underline{CH}{=}CH{-}CO{-}$), 5.69 (d, 1H, J = 10 Hz, $-CH{=}\underline{CH}{-}CO{-}$), 5.17 (m, 1H, $=CH-$), 3.64 (s, 3H, $-O-CH_3$), 2.65 (m, 1H, $-C\underline{H}-CH_3$), 2.53 (ddd, 1H, J = 10, J' = 6, J" = 2 Hz, C-4a H), 1.57 (br.s, 3H, $=C-CH_3$), 1.13 (d, 3H, J = 7 Hz, $-CH-C\underline{H}_3$), and 1.10 (s, 6H, 2X$-CH_3$); ir 1728 (ester C=O), 1689 (enone C=O), 1374 (CH_3), and 729 cm^{-1} (C=CH); ms M^+ 262.1567 (calcd. for $C_{16}H_{22}O_3$: 262.1569). Anal. Calcd. for $C_{16}H_{22}O_3$: C 73.25, H 8.45; Found: C 72.91, H 8.61.

4,4,6,8α-Tetramethyl-4aβ,5,8,8aβ-tetrahydro-1(4H)-naphthalenone (33) and 4,4,6,8α-Tetramethyl-4aβ,5,8,8aα-tetrahydro-1(4H)-naphthalenone (38) from Keto-ester 75

Keto-ester 75 (62 mg, 0.24 mmol) was dissolved in 2,4,6-collidine (2 ml) under an atmosphere of argon. Anhydrous lithium iodide (192 mg, 1.43 mmol) and water (51 μl, 51 mg, 2.85 mmol) were added and the mixture was heated at reflux for 90 min. The reaction mixture was then cooled to room temperature, poured into cold aqueous 5% hydrochloric acid and extracted with ether. The extracts were washed with aqueous 5% hydrochloric acid and water, dried, filtered and concentrated. Column chromatography on silica gel, eluting with 2-5% ether in petroleum ether, gave a 65:35 mixture of *cis*- and *trans*-enones 33 and 38 (16 mg, 35% yield).

4,4,6,8β-Tetramethyl-4aβ,5,8,8aβ-tetrahydro-1(4H)-naphthalenone (63) and 4,4,6,8β-Tetramethyl-4aβ,5,8,8aα-tetrahydro-1(4H)-naphthalenone (79)

Keto-ester 76 (112 mg, 0.43 mmol) was dissolved in 2,4,6-collidine (2 ml) under an atmosphere or argon. Anhydrous lithium iodide (343 mg, 2.56 mmol) and water (92 μl, 92 mg, 5.12 mmol) were added and the mixture was heated at reflux with vigorous stirring. After 2 hr. the mixture was cooled to room temperature, poured into cold aqueous 5% hydrochloric acid and extracted with ether. The extracts were washed with aqueous 5% hydrochloric acid and water, dried, filtered and concentrated. Column chromatography of the residue on silica gel, eluting with 2-5% ether in petroleum ether, gave a 55:45 mixture of *cis*- and *trans*-enones 63 and 79 (73 mg, 83% yield). The nmr spectrum showed two sets of signals; one assignable to *cis*-enone 63: δ6.25 (dd, ~1/2H, J = 10, J' = 2 Hz, –CH=CH–CO–), 5.67 (d, ~1/2H, J = 10 Hz, –CH=CH–CO–), 5.38 (d, ~1/2H, J = 5 Hz, =CH–), 2.97 (qm, ~1/2H, J = 7 Hz

$-\overset{|}{C}\underline{H}-CH_3$), 2.46 (d, $\sim$1/2H, J = 4 Hz, $-\overset{|}{C}H-CO-$), 1.56 (br.s, 3X $\sim$1/2H, $=\overset{|}{C}-CH_3$), 1.28 (s, 3X $\sim$1/2H, $-CH_3$), 1.11 (s, 3X $\sim$1/2H, $-CH_3$), and 0.97 (d, 3X $\sim$1/2H, J = 7 Hz, $-\overset{|}{C}H-\underline{CH_3}$); the other assignable to the *trans*-enone 79: δ6.57 (d, $\sim$1/2H, J = 10 Hz, $-\underline{CH}=CH-CO-$), 5.73 (d, $\sim$1/2H, J = 10 Hz, $-CH=\underline{CH}-CO-$), 5.23 (m, $\sim$1/2H, $=CH-$), 2.77 (qm, $\sim$1/2H, J = 7 Hz, $-\overset{|}{C}\underline{H}-CH_3$), 1.64 (br.s, 3X $\sim$1/2H, $=\overset{|}{C}-CH_3$), 1.16 (s, 3X $\sim$1/2H, $-CH_3$), 1.02 (s, 3X $\sim$1/2H, $-CH_3$), and 0.75 (d, 3X $\sim$1/2H, J = 7 Hz, $-\overset{|}{C}H-C\underline{H_3}$). The following data were recorded on the mixture of 63 and 79: ir 1681, 1670 (C=O), 1395, 1377, 1366 (CH_3), 840 cm^{-1} (C=CH); ms M^+ 204.1518 (calcd. for $C_{14}H_{20}O$: 204.1514).

4,4,6,8-Tetramethyl-1(4H)-naphthalenone (43) from Keto-ester 76

A 55:45 mixture of *cis*- and *trans*-enones 63 and 79 (72 mg, 0.35 mmol) was dissolved in carbon tetrachloride (10 ml) and *N*-bromosuccinimide (125 mg, 0.71 mmol) and benzoyl peroxide (5 mg, 0.02 mmol) were added. The mixture was heated at reflux for 1 hr. then cooled to room temperature, filtered and concentrated. Column chromatography of the residue on silica gel, eluting with 0.5% ether in petroleum ether, gave aryl-ketone 43 (22 mg, 31% yield).

General Conditions for Lewis Acid Catalysed Reaction of Dienone-ester 64 with Isoprene (Table XI)

Dienone-ester 64 (95 mg, 0.52 mmol) was dissolved in anhydrous ether (5 ml). The Lewis acid catalyst (0.26 mmol) was added and after

5-10 min. isoprene (1.04 ml, 10.4 mmol) was added. The progress of the reaction was followed by tlc and gc (Column A). After completion of the reaction saturated aqueous sodium bicarbonate (∿2 ml) was added and the mixture extracted with ether. The extracts were washed with water, dried, filtered and concentrated. In several cases (see Table XI) the residue was purified by column chromatography on silica gel, eluting with 8-20% ether in petroleum ether. The crude residues or purified products were analysed by gc (Column A) and the product ratios (72:73, Table XI) were determined by integration of the gc peaks. In the case of the boron trifluoride etherate (Entry 19) and stannic chloride (Entry 31) catalysed reactions, the principal products (73 and 72 respectively) were easily obtained pure by fractional crystallization from the product mixtures.

REFERENCES

1. A.S. Onishchenko, "Diene Synthesis", Israel Program for Scientific Translation, Jerusalem, 1964.
2. Yu.A. Titov, Russ. Chem. Rev., 31, 267 (1962).
3. K. Alder and G. Stein, Angew. Chem., 50, 510 (1937).
4. J. Sauer, Angew. Chem. Int. Ed. Engl., 5, 211 (1966).
5. J. Sauer, Angew. Chem. Int. Ed. Engl., 6, 16 (1967).
6. J.G. Martin and R.K. Hill, Chem. Rev., 61, 537 (1961).
7. K. Alder, "Nobel Lectures in Chemistry 1942-1962", Elsevier, Amsterdam, London, New York, 1964.
8. H.L. Holmes, Organic Reactions, 4, 60 (1948).
9. J.A. Norton, Chem. Rev., 31, 319 (1942).
10. K. Alder in W. Foerst, "Neuere Methoden der Präparativen Organischen Chemie", Verlag Chemie, Berlin, 1943, Vol. 1, p. 251.
11. M.C. Kloetzel, Organic Reactions, 4, 1 (1948).
12. H. Wollweber in Houben-Weyl, "Methoden der Organischen Chemie", Georg Thieme Verlag, Stuttgart, 1970, Vol. 5/ic, p. 977.
13. O. Diels and K. Alder, Ann., 460, 98 (1928).
14. K.N. Houk, Acc. Chem. Res., 8, 361 (1975).
15. R.B. Woodward and R. Hoffmann, Angew. Chem. Int. Ed. Engl., 8, 781 (1969).
16. K.N. Houk, J. Amer. Chem. Soc., 95, 4092 (1973).
17. K.N. Houk and R.W. Strozier, J. Amer. Chem. Soc., 95, 4094 (1973).
18. M.J.S. Dewar, A.C. Griffin and S. Kirschner, J. Amer. Chem. Soc.,

96, 6220 (1974).

19. G. Stork, E.E. van Tamelen, L.F. Friedman and A.W. Burgstahler, J. Amer. Chem. Soc., 75, 384 (1953).
20. R.B. Woodward, F. Sondheimer, D. Taub, K. Heusler and W.M. McLamore, J. Amer. Chem. Soc., 74, 4223 (1952).
21. L.H. Sarett, G.E. Arth, R.M. Lukes, R.E. Beyler, G.I. Poos, W.F. Johns and J.M. Constantin, J. Amer. Chem. Soc., 74, 4974 (1952).
22. J.E. Cole, W.S. Johnson, P.A. Robins and J. Walker, J. Chem. Soc., 244 (1962).
23. R.B. Woodward, R.E. Bader, H. Bickel, A.J. Frey and R.W. Kierstead, Tetrahedron, 2, 1 (1958).
24. K. Alder, G. Stein, F. von Bruddenbrock, W. Eckardt, W. Frercks and S. Schneider, Ann., 514, 1 (1934).
25. K. Alder and W. Vogt, Ann., 571, 137 (1951).
26. A.A. Petrov and N.P. Sopov, Zhurnal Obshchei Khimii, 25, 517 (1955).
27. A.A. Petrov and N.P. Sopov, Zhurnal Obshchei Khimii, 22, 591 (1952).
28. I. Fleming, F.L. Gianni and T. Mah, Tetrahedron Letters, 881 (1976).
29. P.D. Bartlett and G.F. Woods, J. Amer. Chem. Soc., 62, 2933 (1940).
30. P. Yates and P. Eaton, J. Amer. Chem. Soc., 82, 4436 (1960).
31. G.I. Fray and R. Robinson, J. Amer. Chem. Soc., 83, 249 (1961).
32. T. Inukai and M. Kasai, J. Org. Chem., 30, 3567 (1965).
33. T. Inukai and T. Kojima, J. Org. Chem., 32, 869 (1967).
34. E.F. Lutz and G.M. Bailey, J. Amer. Chem. Soc., 86, 3899 (1964).
35. T. Inukai and T. Kojima, J. Org. Chem., 31, 1121 (1966).

36. T. Inukai and T. Kojima, J. Org. Chem., 31, 2032 (1966).

37. F. Fringuelli, F. Pizzo, A. Taticchi and E. Wenkert, Syn. Comm., 9, 391 (1979).

38. I. Nagakura, H. Ogata, M. Ueno and Y. Kitahara, Bull. Chem. Soc. Japan, 48, 2995 (1975).

39. R.L.N. Harris, F. Komitsky and C. Djerassi, J. Amer. Chem. Soc., 89, 4765 (1967).

40. J.N. Marx and L.R. Norman, Tetrahedron Letters, 2867 (1973).

41. H.E. Zimmerman, P. Hackett, D.F. Jones, J.M. McCall and B. Schroder, J. Amer. Chem. Soc., 93, 3653 (1971).

42. R.A. Barnes, J. Amer. Chem. Soc., 70, 145 (1948).

43. H.J. Liu and E.N.C. Browne, Can. J. Chem., 57, 377 (1979).

44. R.B. Carlin and K.P. Sivaramakrishna, J. Org. Chem., 35, 3368 (1970).

45. H.J. Liu ~~and E.~~N.C. Browne, Can. J. Chem., 96, 306 (1978).

46. R.M. Silverstein and G.C. Bassler, "Spectrometric Identification of Organic Compounds" 2nd ed., Wiley, New York, 1967.

47. L.M. Jackman and S. Sternhell, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry", 2nd ed., Pergamon, Oxford, 1969.

48. G.V. Pigulevskii, V.I. Kovaleva, and D.V. Motuskus, Voprosy Khimii Terpenov i Terpenoidov Akad. Nauk. Litovsk S.S.R. Trudy Vsesoyuz Soveshchaniya Vil'nyus, 153 (1959).

49. T.R. Kemp, L.P. Stoltz and L.V. Packett, Phytochemistry, 10, 478 (1971).

50. F.S. Edmunds and R.A.W. Johnstone, J. Chem. Soc., C, 2892 (1965).

51. K. Kawashima and T. Yamanishi, Nippon Nogei Kagaku Kaishi, 47, 79 (1973).

52. E. Piers and W.M. Phillips-Johnson, Can. J. Chem., 53, 1281 (1975).

53. W. Nagata and H. Itazaki, Chemistry and Industry, 1194 (1964).

54. M.T. Bogert and V.G. Fourman, J. Amer. Chem. Soc., 55, 4670 (1933).

55. P.A. Robins and J. Walker, J. Chem. Soc., 642 (1952).

56. W.C. Still, M. Kahn and A. Mitra, J. Org. Chem., 43, 2923 (1978).

57. M.J.S. Dewar in P. de Mayo, "Molecular Rearrangements", part 1, Wiley, New York, 1963, page 295.

58. H.J. Liu and E.N.C. Browne, Tetrahedron Letters, 2919 (1977).

59. E.J. Corey, R.B. Mitra and H. Uda, J. Amer. Chem. Soc., 86, 485 (1964).

60. F. Elsinger, Org. Syn., 45, 7 (1965).

61. J.B. Stothers "Carbon-13 NMR Spectroscopy", Academic Press, New York, 1972.

62. D.P.N. Satchell and R.S. Satchell, Chem. Rev., 69, 251 (1969).

63. P.M. Druce, M.F. Lappert and P.N.K. Riley, J. Chem. Soc., Chem. Comm., 486 (1967).

64. R.G. Pearson and J. Songstad, J. Amer. Chem. Soc., 89, 1827 (1967).

65. J.J. Myher and K.E. Russel, Can. J. Chem., 42, 1555 (1964).

66. Z. Strojonac, R.A. Dickinson, N. Strojanac, R.J. Woznow and Z. Valenta, Can. J. Chem., 53, 616 (1975).

67. M. Kakushima, J. Espinosa and Z. Valenta, Can. J. Chem., 54,

3305 (1976).

68. F.A. Cotton and G. Wilkinson, "Advanced Inorganic Chemistry", 2nd ed., Wiley, New York, 1966.

69. G. Zweifel and H.C. Brown, Organic Reactions, 13, 28 (1963).

70. L.F. Fieser and M. Fieser, "Reagents for Organic Synthesis", Vol. 1, Wiley.

71. E. Benzing, Angew. Chem., 71, 521 (1959).

72. H.J. Liu and I.V. Oppong, unpublished results.

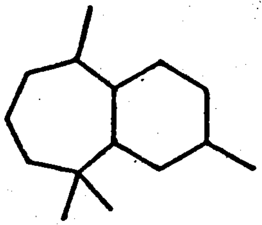
73. S.R. Milstein and E.A. Coates, Aldrichimica Acta, 11, 10 (1978).

CHAPTER 2

Total Synthesis of α- and β- Himachalene and Synthetic Studies on Isohimachalone

Introduction

The himachalane carbon skeleton (1) is characteristic of a relatively new but growing class of sesquiterpenes. The isolation of two representatives of the class was first reported by Dev in 1952 from the essential oil of the Himalayan cedar (*Cedrus deodara Loud*)[1]. The gross skeletal structure of the two new hydrocarbons, which were designated α- and β-himachalene were reported almost simultaneously in 1961 by Dev[2] and by Erdtman[3] who isolated the two compounds from Atlas cedar (*Cedrus atlantica*) and from *Cedrus libani*. In 1968 Dev was able to rigorously establish the structure[4] and the absolute stereochemistry[5] of α-himachalene as 2 and of β-himachalene as 3.



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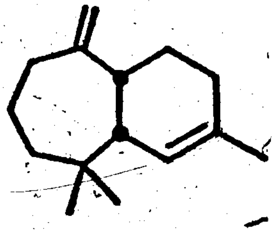

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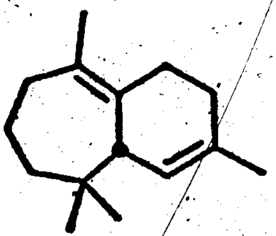

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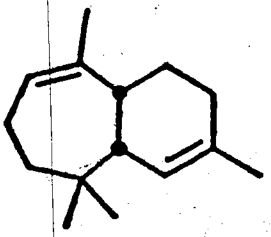
Since then a variety of compounds of the himachalane class have been reported. Among them are γ-himachalene (4)[6,7,8] and the aromatic hydrocarbons *ar*-himachalene (5)[4] and 7,8-dehydro-*ar*-himachalene (6)[6,8].



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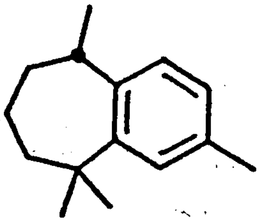

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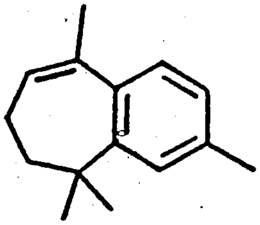

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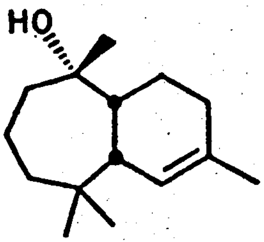
A number of oxygenated derivatives have also been reported: himachalol (7)[1,9], two epimeric epoxides 8[6,8,10], and 9[10], oxidohimachalene (10)[11], centdarol (11)[12], and isocentdarol (12)[13].



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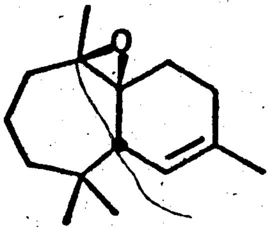

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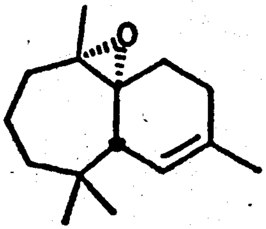

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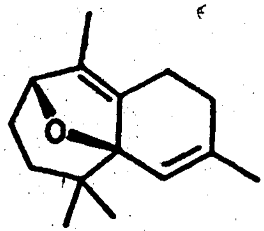

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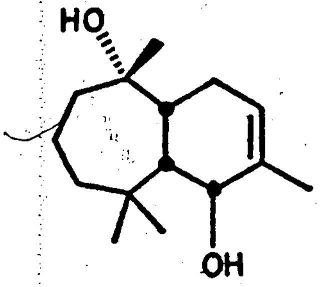

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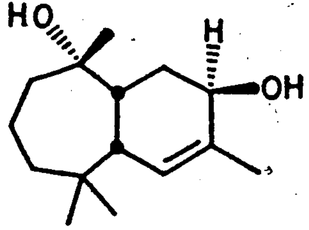

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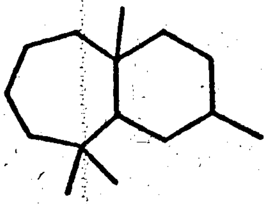
Recently two other very closely related skeletal types have been reported. The isohimachalane skeleton (13) is characteristic of two reported compounds. Teisseire has reported the isolation[6] of a ketone from *Cedrus atlantica* to which he has assigned the *trans*-fused structure 14[14]. And Dev[15] has reported the isolation from *Cedrus deodara Loud.* of a ketone to which he has assigned *cis*-fused structure 15 and which he has named isohimachalone. The allohimachalane



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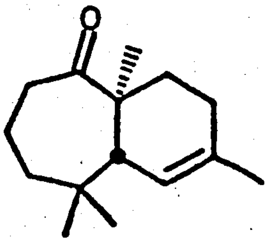

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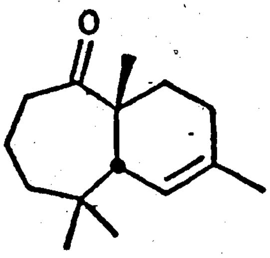

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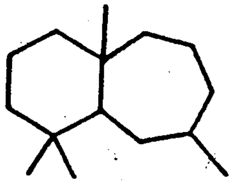
skeleton (16) is characteristic of two compounds isolated by Dev from *Cedrus deodara Loud.*: allohimachalol (17)[16,17] and allohimachalone (18)[15].



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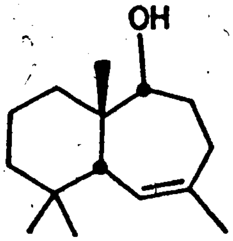

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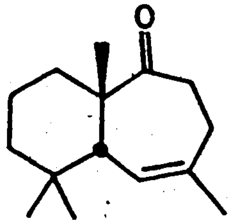

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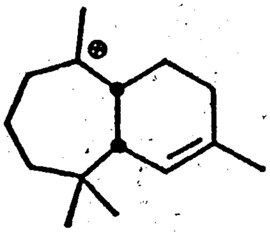
The cation 19 has been proposed[2,3,18] as the biogenetic precursor of the himachalane structural class. Elimination of a proton from 19 would give α- (2), β- (3), or γ-himachalene (4) while addition of a water molecule followed by deprotonation would give himachalol (7). A Wagner-Meerwein shift[19] in cation 19 could give cation 20 as a possible precursor to the allohimachalane class[*].



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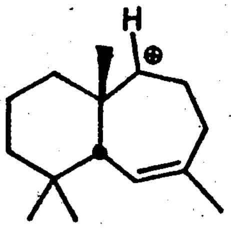

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It has been suggested[14] that *trans*-ketone 14 arises by a rearrangement of the epoxide 9. The epimeric epoxides 8 and 9 are

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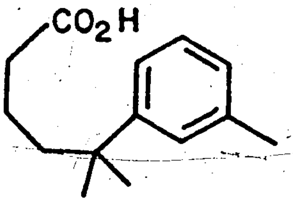
[*] Solvolysis of the tosylate of allohimachalol (17) gives both allohimachalol (17) and himachalol (7)[17].

reportedly[20] auto-oxidation products of β-himachalene (3) so conceiveably the *cis*-ketone 15 (isohimachalone) could arise via a similar rearrangement of the naturally occurring epoxide 8. In an analagous manner allohimachalone (18) could arise via rearrangement of epoxide 9[20].

Previous synthetic approaches to the himachalane skeleton include two syntheses of *ar*-himachalene (5) by Dev[21]. In one approach the key step involved intramolecular cyclization of the aromatic acid 21 to give ketone 22 which was easily converted to 5. In the other, intramolecular Friedel-Crafts alkylation of (+)-*ar*-turmerone (23) gave (+)-cyclo-*ar*-turmerone (24) which was then converted to (+)-*ar*-himachalene (5).



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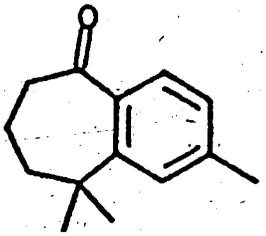

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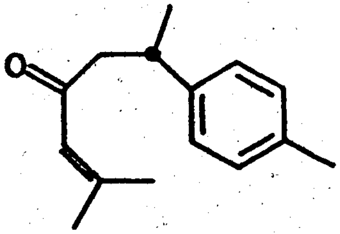

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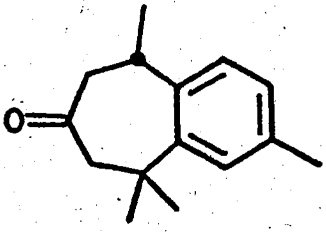

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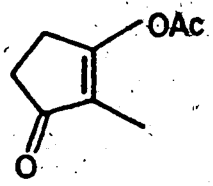
The total synthesis of β-himachalene (3) was first reported by de Mayo using a photochemical approach[22,23]. The 2πs + 2πs cycloaddition of enol acetate 25 with ketal 26 gave tricyclic adduct 27.



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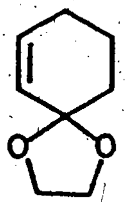

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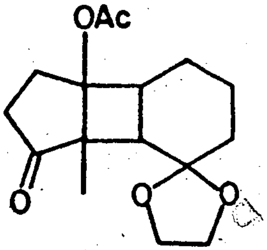

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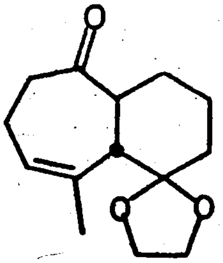
Reduction of the ketone in 27 and mesylation of the resulting alcohol followed by base catalysed ring opening gave ketone 28. Ketone 28 was converted in seven steps to two epimeric diols 29 each of which could be converted by phosphoryl chloride dehydration to a mixture of



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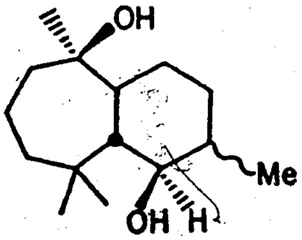

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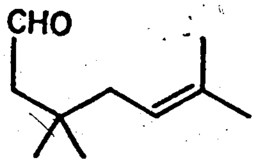
hydrocarbons which included β-himachalene (3) (8% of the reaction product). The overall yield of β-himachalene (3) was 0.21% in thirteen steps from enol-acetate 25.

The first synthesis of α-himachalene (2) was reported in a short communication by Wenkert[24] who used an intramolecular Diels-Alder approach. The aldehyde 30 prepared[25] in two steps from diol 31 was converted to the key intermediate 32 in nine steps. Cyclization of 32 in refluxing toluene with aluminum chloride as a catalyst gave the ketone 33. A Wittig reaction on 33 gave α-himachalene (2).



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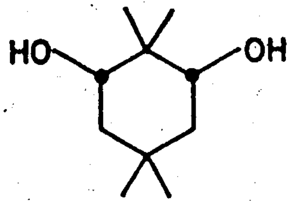

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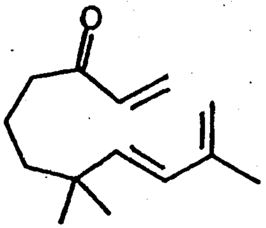

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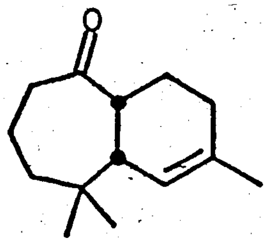

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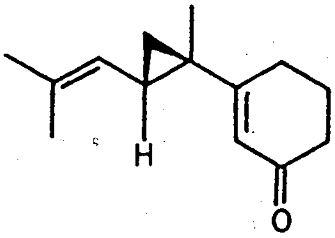
Treatment of 33 with methyl lithium followed by dehydration of the resulting alcohol with phosphoryl chloride in pyridine gave an 80:20 mixture of α-himachalene (2) and β-himachalene (3).

Recently β-himachalene was synthesized by Piers[26] using a Cope rearrangement of a 1,2-divinyl-cyclopropane derivative. The key intermediate 34 was prepared in seven steps from acrolein and treatment of 34 in refluxing xylene for 3 hr. gave the fused bicyclic ketone 35. Regioselective methylation of ketone 35 followed by reduction of the disubstituted double bond and removal of the ketone carbonyl via enol-phosphate 36 gave β-himachalene (3) in 34% yield over the five steps from 34.



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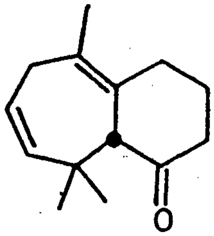

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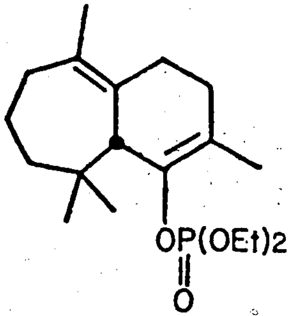

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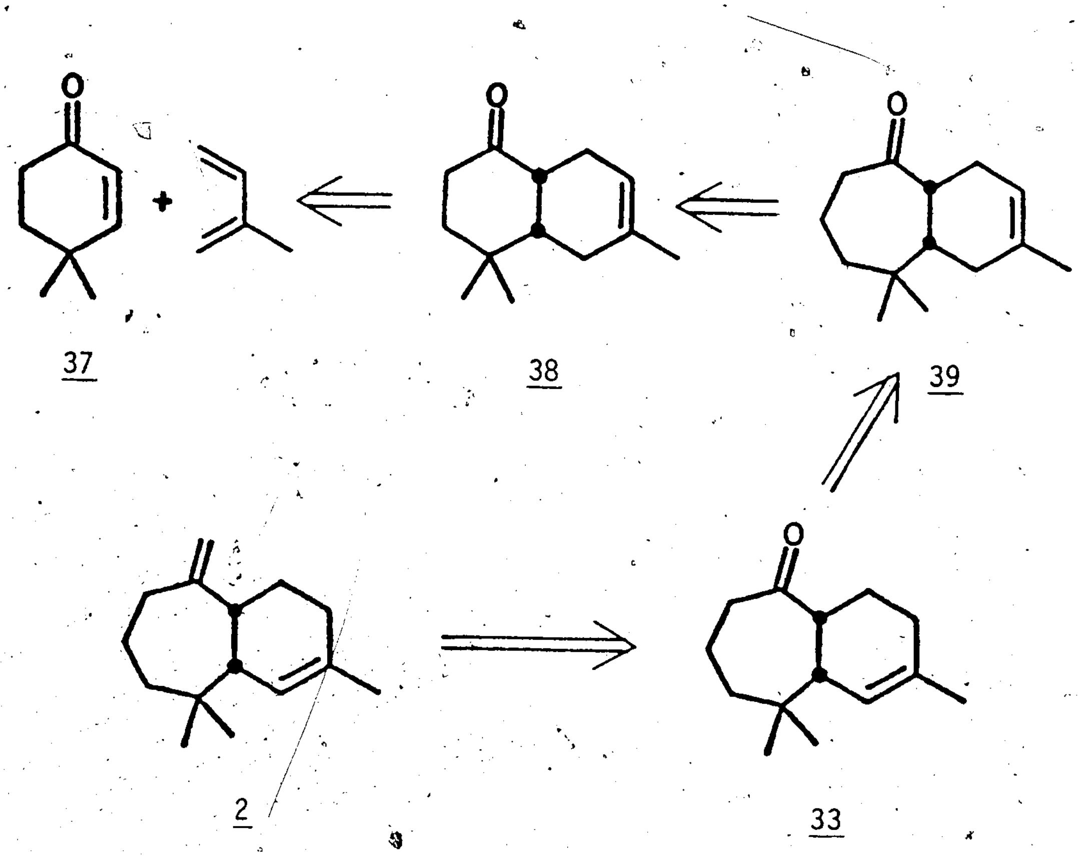
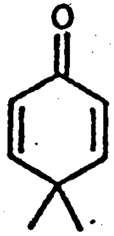
A modern synthetic scheme should be designed to achieve the rapid assembly of the target carbon skeleton in an intermediate containing functional groups which require only simple modifications to give the synthetic target. On this basis, the assembly of the himachalane ring system could be obtained via a Diels-Alder addition of isoprene to enone 37. One carbon ring expansion of the resulting adduct 38 should give an intermediate 39 which requires only double bond isomerization to 33 and conversion of the ketone carbonyl to a vinylidene group to complete the synthesis of α-himachalene (2).

The study of the Diels-Alder reactions of 4,4-dimethylcyclohexenone systems (Chapter 1 of this thesis) has shown that neither enone 37 nor dienone 40 are suitable as starting points for the synthesis of α-himachelene. Enone 37 is virtually inert to cycloaddition and dienone 40 gives exclusively the ketone (41)[27] with the ring B methyl





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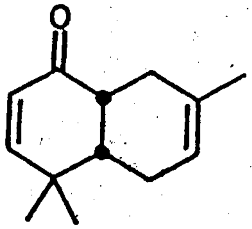

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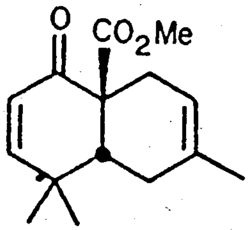
substituent in the wrong position. The same study however, demonstrated that an intermediate with the correct regiochemistry--keto-ester 42--could be constructed by a Diels-Alder addition of isoprene to keto-ester 43. Potentially ketone 38 could be obtained from 43 by a reduction of the enone double bond and decarbomethoxylation.



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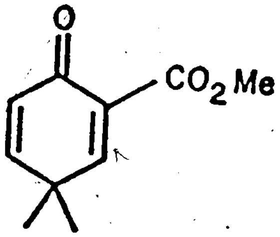
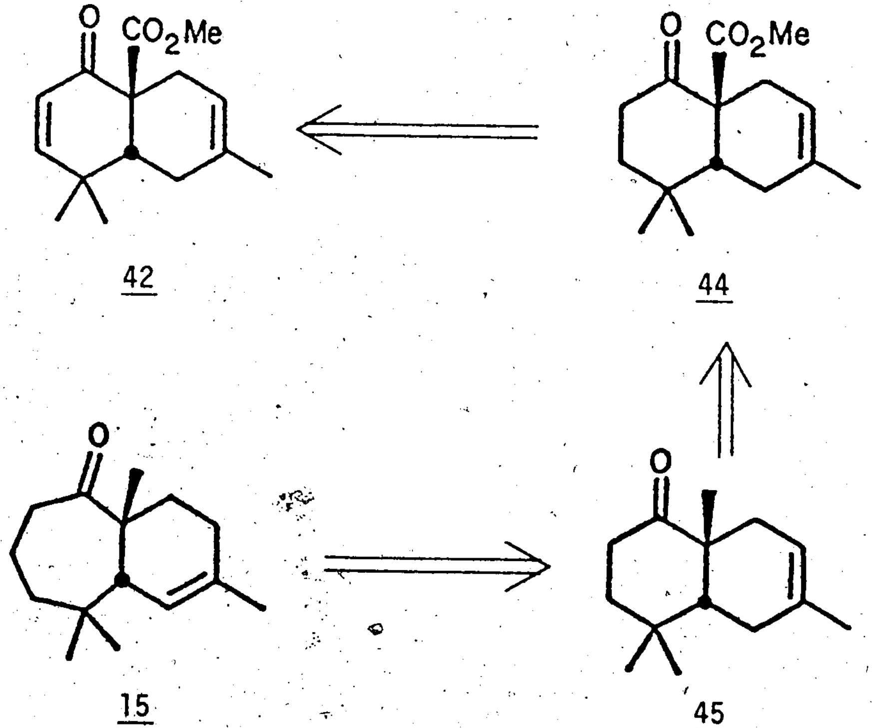
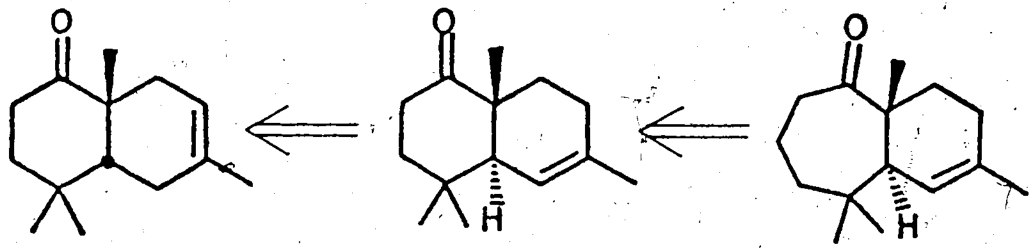


43

Keto-ester 42 also offers a suitable starting point for synthesis of the isohimachalane skeleton. Reduction to saturated ketone 44 followed by conversion of the carbomethoxyl substituent to an angular methyl group would give ketone 45 which requires only homologation of the A ring and isomerization of the double bond to give *cis*-ketone 15, the assigned[15] structure of isohimachalone.

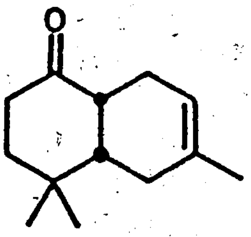


A similar approach could be applied to the synthesis of *trans*-ketone 14. Starting with the *cis*-fused ketone 45, isomerization of the double bond and epimerization of the ring junction could give *trans*-fused ketone 46 which, after homologation of the A ring, would give the ketone 14.



45 46 14

The total synthesis of α-himachalene (2) and β-himachalene (3) has been achieved by a highly efficient route based on the synthetic strategy outlined above. The synthesis of *cis*-ketone 15 has also been achieved and found to be not identical with naturally occurring isohimachalone. The synthesis of *trans*-ketone 14 is under study and the progress in this study will be reported.



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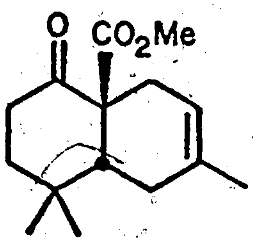
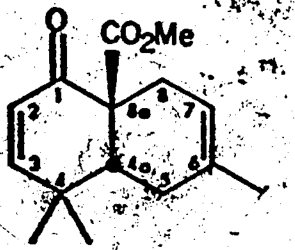


44

Results and Discussion

α- and β-Himachalene

The Diels-Alder adduct 42, the structure of which has been conclusively demonstrated (see Chapter 1 of this thesis), was employed as the key synthetic intermediate for the synthesis of α-himachalene (2) and β-himachalene (3) according to the scheme outlined in the introduction. The conversion of keto-ester 42 to ketone 38 was conveniently approached via the saturated ketone 44 which was also an intermediate in the proposed synthesis of the isohimachalane skeleton (13).



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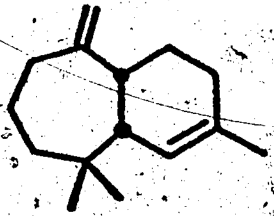

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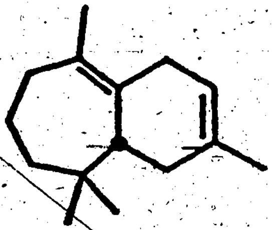

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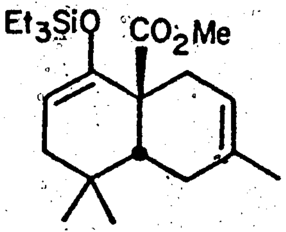
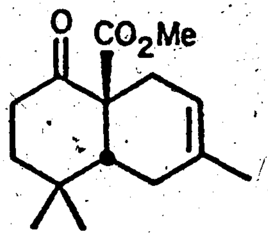
In the presence of Wilkinson's catalyst (*tris*-triphenylphosphine rhodium(I) chloride)[28] hydrosilanes have been shown[29] to add to α,β-unsaturated ketones exclusively by 1,4-addition to give silyl enol-ethers which readily undergo hydrolysis[30] to give saturated ketones. When enone 42 as a 25% solution in benzene was treated with triethylsilane and a catalytic amount of Wilkinson's catalyst, only a small amount of addition product was observed after 5 days. However when finely divided solid keto-ester 42 was suspended in triethylsilane in the presence of the catalyst, conversion to product was complete within 24 hr. The purified product, obtained in 91% yield was identified as silyl enol-ether 47. Hydrolysis of 47 with potassium carbonate in aqueous methanol gave the saturated ketone 44 in 88% yield. The crude silyl enol-ether 47 could conveniently be hydrolysed to give keto-ester 44 in 94% yield from keto-ester 42.



47

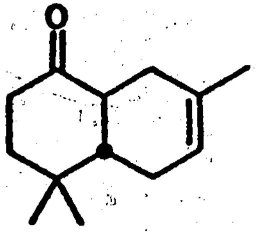


44

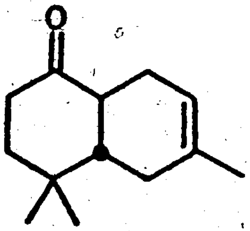
The saturated ketone 44 showed a molecular ion at m/e 250.1570 in the mass spectrum indicating the chemical formula $C_{15}H_{22}O_3$. The ir spectrum showed bands at 1743 and 1710 cm^{-1} due to a saturated ester and a saturated ketone respectively. The nmr spectrum showed a multiplet at δ5.32 due to a vinyl proton and methyl groups appeared as singlets at δ3.67 (ester), 1.63 (allylic), 1.09 and 0.99.

Keto-ester 44 was decarbomethoxylated with lithium iodide dihydrate in refluxing 2,4,6-collidine[31] to give two products in 94% yield and in a ratio of ~80:20 (90:10 on one occasion) which were easily separated by column chromatography on silica gel.

The major isomer showed a molecular ion at m/e 192.1513 in the mass spectrum indicating the chemical formula $C_{13}H_{20}O$. The ir spectrum showed a band due to a saturated ketone at 1706 cm^{-1}. The nmr spectrum showed a vinyl proton signal as a broad singlet at δ5.33, an allylic methyl as a singlet at δ1.61 and two other methyl singlets at δ1.07 and 0.98. Comparison of the nmr (Table I) and cmr specta (Table II) with those of the known *trans*-ketone 48[27] indicated that the major product was the *trans*-ketone 49.



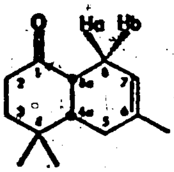
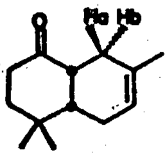
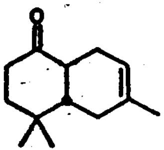
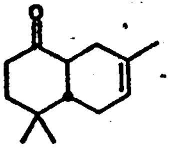
48



49

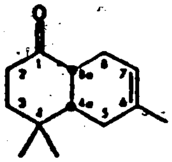
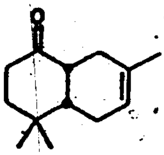
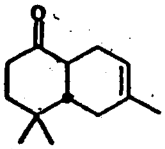
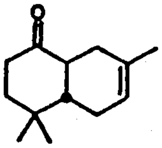
The minor isomer showed a molecular ion at m/e 192.1522 ($C_{13}H_{20}O$) in the mass spectrum and the ir spectrum showed a ketone absorption

TABLE I. NMR Spectra (δ) of Ketones 38, 48, 49 and 50

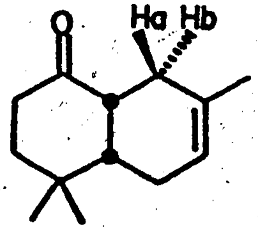
	 38	 50	 49	 48
C-8 Hb	2.50	2.40	a	a
C-8a H	2.81	2.89	a	a
vinylic CH_3	1.58	1.65	1.61	1.65
vinyl H	5.22	5.17	5.33	5.24
gem CH_3	1.32	1.32	1.07	1.07
	0.98	0.98	0.98	0.99

[a] The signal for this proton was not clearly defined in the spectrum.

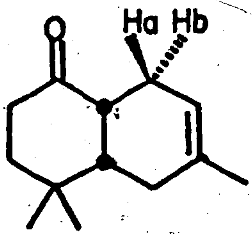
TABLE II. CMR Spectra (δ) of Ketones 38, 48, 49 and 50

	 20	 50	 49	 48
C-1	211.9	211.1	212.8	212.2
C-2	35.6	35.6	38.9	38.2
C-3	37.9	37.8	42.2	41.4
C-4	33.0	33.0	33.3	32.5
C-4a	46.6	46.0	48.3	47.2
C-5	29.3	24.7	32.5	27.0
C-6	121.4	118.8	133.1	119.5
C-7	118.9	131.8	120.2	132.3
C-8	24.1	28.7	26.3	30.2
C-8a	43.6	44.5	46.0	45.7
vinylic CH_3	23.7	23.2	24.2	23.3
gem CH_3 {	26.9 27.8	26.9 28.0	20.0 29.7	19.4 29.0

at 1709 cm^{-1}. The nmr spectrum showed a vinyl proton as a broad singlet at δ5.22 and methyl groups at δ1.58, 1.32 and 0.98. Comparison of the nmr and cmr spectra with those of the known *cis*-ketone <u>50</u>[27] indicated that the minor product was the *cis*-ketone <u>38</u>.



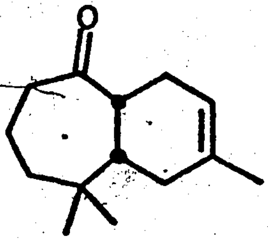
<u>50</u>



<u>38</u>

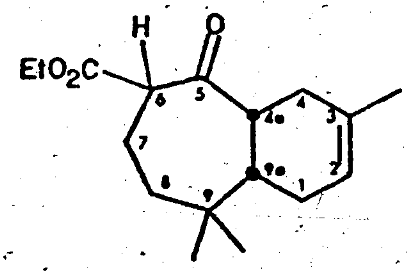
In proof of the stereochemical assignment, *cis*-ketone <u>38</u> was epimerized with sodium hydroxide in aqueous methanol to give an equilibrium mixture of <u>49</u> and <u>38</u> in a ratio of 82:18 and in 95% yield.

The most direct approach to α-himachalene (<u>2</u>) from this point would appear to require homologation of *cis*-ketone <u>38</u> to the ketone <u>39</u>.



<u>39</u>

The ring expansion of ketones with ethyl diazoacetate[32] has been shown[33,34] to proceed via the selective migration of the less substituted carbon α to the carbonyl group. During the course of an unsuccessful synthesis of α-himachalene (2) the ring expansion of *cis*-ketone 50[27] was examined. Both ring expansion products 51 and 52 were obtained in a 50:50 ratio and in poor yield (39% total). Ring expansion of the *trans*-ketone 48[27], on the other hand, readily (0°, 1 hr.) gave *trans*-fused ring expansion products 53 and 54 (90:10) in a total yield of 85%. On the basis of these results the direct homologation did not appear to offer an efficient route to the



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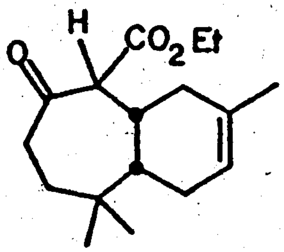

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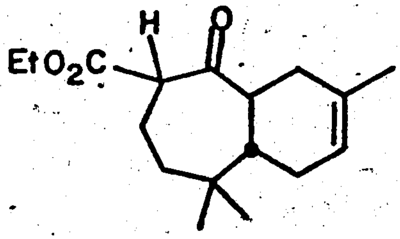

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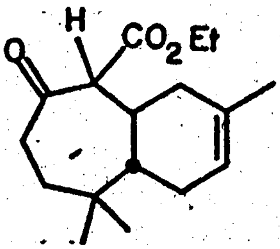
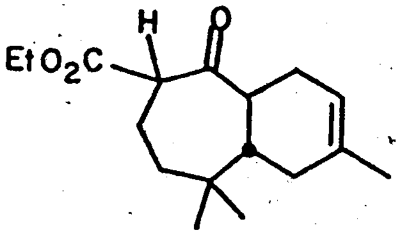


54

himachalane skeleton (1). Furthermore the *cis*-ketone 38 was obtained only as a minor product of decarboxylation of 44 and efficient use of the starting materials would require successive epimerizations of 49 followed by chromatographic separation of the minor component 38. With these difficulties in mind it seemed more expedient to proceed with ring expansion of the major isomer, *trans*-ketone 49 and to correct the ring junction stereochemistry at a later stage.

Treatment of 49 with ethyl diazoacetate and boron trifluoride etherate at 0° for 1 hr. gave two chromatographically separable products. The major product, obtained in 90% yield showed a molecular ion at m/e 278.1883 in the mass spectrum indicating the chemical formula $C_{17}H_{26}O_3$. The ir spectrum showed an absorption due to a ketone in a seven membered ring at 1703 cm^{-1} and a band at 1746 cm^{-1} due to an ester group. The nmr spectrum showed a vinyl proton as a broad singlet at δ5.33. The ethyl ester gave a pair of methylene quartets (one proton each) at δ4.08 and 4.06 and a methyl triplet at δ1.21. A *gem*-dimethyl group appeared as singlets at δ0.95 and 0.76 and an allylic methyl group gave a singlet at δ1.65. A signal at δ3.53 was characteristic of a methine proton on the α-carbon of a β-keto ester. The signal was a doublet of doublets with coupling constants of 10 Hz and 4 Hz indicating the presence of two adjacent protons. These data were consistent with the assignment of structure 55 to the major product.

The minor product, obtained in 10% yield showed spectral features



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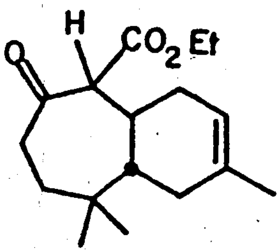
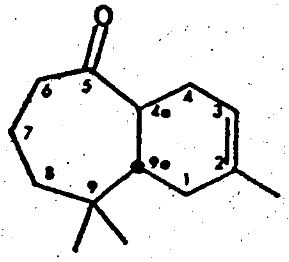


56

very similar to those obtained for keto-ester 55. The mass spectrum gave a molecular ion at m/e 278.1886 ($C_{16}H_{26}O_3$) and the ir spectrum showed typical seven membered ring ketone (1706 cm^{-1}) and saturated ester (1750 cm^{-1}) absorptions. The nmr spectrum showed a vinyl proton at δ5.27, an ethyl ester group as a quartet at δ4.10 and a triplet at δ1.25, and three other methyl groups at δ1.63, 1.02 and 0.81. In this case however, the nmr signal at δ3.28, indicating one proton at the α-carbon of a β-keto ester, was a doublet with a coupling constant of 8 Hz indicating the presence of only one adjacent proton. This was consistent with the assignment of structure 56 to the minor product. Both 55 and 56 were single compounds (17 lines in their cmr spectra) existing exclusively in the keto-form. The stereochemistry at the newly introduced chiral center, however, could not be assigned with certainty.

Keto-ester 55 was decarboxylated with lithium iodide dihydrate[31] to give ketone 57 in 85% yield. The nmr spectrum of 57 was identical with previously reported[35] nmr data for 57 obtained by degradation of α-himachalene (2).

The synthesis of the key intermediate 33 from ketone 57 requires two operations. In one, the double bond must be moved from the C-2 to the C-1 position. In the other, the stereochemistry of the ring junction must be converted from *trans* to *cis*. Dev[35] has reported that ketone 58, when treated with oxalic acid in aqueous



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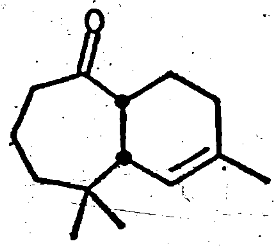

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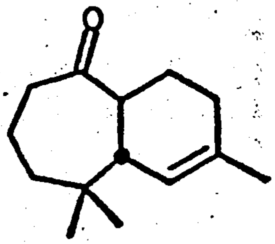

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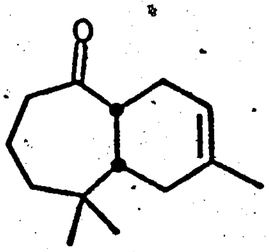

39

dioxan at reflux for 12 hr., produces an equilibrium mixture of 58 and 59 in a ratio of 15:85 (determined by gc analysis). Furthermore it has been reported by Wenkert[24] that the ketone 33, when subjected to base catalysed equilibration (conditions unspecified), gives a 50:50 equilibrium distribution* with its *trans*-isomer <u>58</u>. The sequential application of these two equilibration conditions appeared to offer an acceptable route from <u>57</u> to <u>33</u>.

It was found, however, that application of Dev's oxalic acid equilibrating conditions to ketone <u>57</u> produced no detectable trace of any isomeric ketone and the starting material was recovered quantitatively. The application of more strongly acidic conditions was investigated. In refluxing benzene with *p*-toluenesulfonic acid an equilibrium was rapidly established within 1 hr., as determined by gc analysis. Two peaks were observed in a ratio of 65:35. The minor component had a retention time identical with that observed for pure ketone <u>57</u> while the major component had a lower retention time. The product mixture was obtained in quantitative yield and nmr analysis showed the presence of four compounds approximately in the ratio 53:27:14:6. Three of these were identified as the known ketones <u>58</u>[35] (53%), <u>57</u>[35] (27%) and <u>33</u>[24] (14%). The fourth, minor component was later shown to be the

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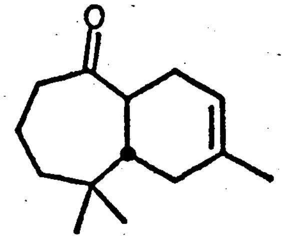
*This result is contradicted by Dev[35] who reports that treatment of <u>58</u> with potassium *t*-butoxide in refluxing *t*-butanol for 5 hr. gives only unchanged starting material as determined by gc and the ir spectrum.

previously unreported *cis*-ketone 39*.



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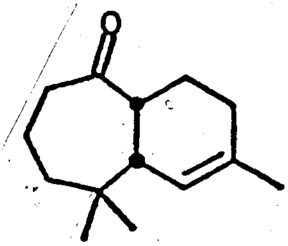

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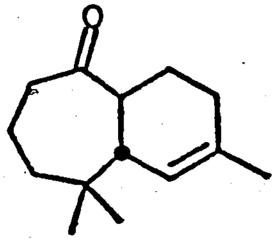

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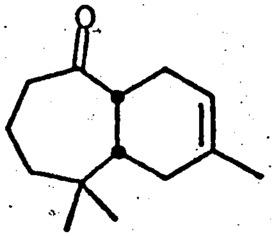

39

Flash chromatography[36] of this mixture on silica gel gave leading

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*The observation of an ~65:35 ratio between *cis*-ketones 33 and 39 and between *trans*-ketones 58 and 57 in this mixture conflicts with Dev's report[35] that an 85:15 equilibrium mixture (58:57) is formed on treatment of 58 with oxalic acid. Our own observation that similar conditions cause no isomerization of *trans*-ketone 57 suggests that such conditions are very slow to promote isomerization and thus in Dev's case equilibrium may not have been reached. It should also be noted that Dev's equilibrium mixture was analysed only by gc. On this basis the possibility cannot be excluded that Dev's conditions also produced quantities of the *cis* isomers 33 and 39 since our own results show that these two compounds are not distinguishable from their respective *trans* isomers 58 and 57 by gc analysis.

fractions of pure *cis*-ketone 33 in approximately 12% yield, and later fractions (in 88% yield) which were a mixture of 58, 33 and 57 as well as the unidentified fourth product. In practice this mixture was subjected sequentially to the acid catalysed equilibration conditions and flash chromatographic removal of the desired *cis*-ketone 33 in order to obtain efficient use of the starting material.

The *trans*-ketone 57 was treated with sodium hydroxide in refluxing aqueous methanol for 48 hr. Gc analysis of the product, obtained in 90% yield, showed one peak identical in retention time with the starting material, however nmr analysis showed the presence of two components in an 80:20 ratio. The major component was identical with the starting ketone 57. The minor component was separated by flash chromatography[36] and was identified as *cis*-ketone 39[*]. Comparison of nmr spectra showed that 39 was the fourth, minor component of the mixture obtained from *p*-toluenesulfonic acid catalysed isomerization of 57.

The epimerization of *cis*-ketone 33 was also examined. Treatment

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[*] The observed 80:20 *trans*:*cis* ratio contradicts Dev's report[35] that equilibration of the *trans* isomer with potassium *t*-butoxide in *t*-butanol at reflux for 5 hr. gave exclusive recovery of the *trans*-fused ketone. Dev's product was analysed by gc, ir and by specific rotation. Since our own results show that the *cis*- and *trans* isomers are inseparable by gc and that the ir spectra are very similar it is possible that Dev obtained, but did not detect, the *cis*-ketone. Alternately it may be possible that under Dev's conditions equilibrium was not established since our own results show that these ketones are quite slow to equilibrate.

of <u>33</u> with sodium hydroxide in refluxing[*] aqueous methanol for 20 hr. gave a product which showed only a single peak on gc analysis. Nmr analysis of the material showed the presence of two compounds in a ratio of 80:20. The minor component was identical with the starting *cis*-ketone <u>33</u>. The major component was identical with the known[35] *trans*-ketone <u>58</u>[**].

The direct conversion of *cis*-ketone <u>33</u> to α-himachalene (<u>2</u>) by a Wittig reaction appeared to be straightforward and has been reported by Wenkert[24]. However it was found that under a variety of conditions the reaction of methylenetriphenylphosphorane with *cis*-ketone <u>33</u> invariably produced only partial conversion of the starting material to a 50:50 mixture of two hydrocarbons which were shown by comparison of nmr spectra with published data to be α-himachalene (<u>2</u>) and the known[22,23,35] hydrocarbon *trans*-α-himachalene (<u>59</u>).

A methylation-dehydration approach proved more effective for the conversion of *cis*-ketone <u>33</u> to himachalenes. As reported by

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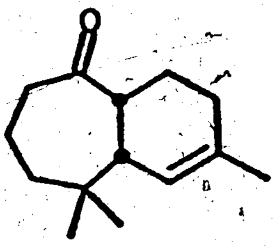
[*] Treatment at room temperature for 24 hr. gave only partial conversion (25%) to *trans*-ketone <u>58</u>.

[**] The observed 80:20 *trans*:*cis* ratio contradicts the report of a 100:0 ratio published by Dev[35] (see details in footnote on Page 165) and also a report by Wenkert[24] of a 50:50 equilibrium ratio obtained from the *cis*-ketone <u>33</u>. Although Wenkert's conditions are not specified it seems possible that in his case equilibrium had not been established.



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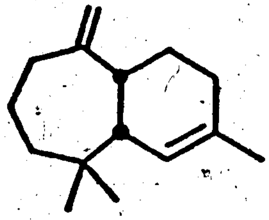

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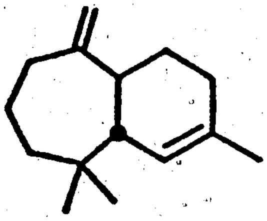

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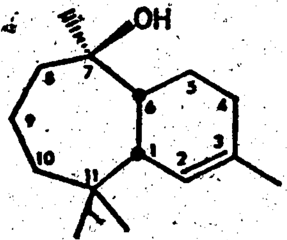
Wenkert[24] the addition of methyl lithium to *cis*-ketone 33 proceeded smoothly and specifically from the less hindered face of the molecule to give 7-*epi*-himachalol (60) in 93% yield. The dehydration of



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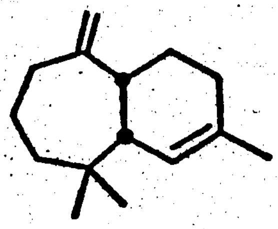
alcohol 60 with one equivalent of phosphoryl chloride in pyridine at room temperature for 24 hr. gave no detectable amount of dehydration product, however use of a large excess of phosphoryl chloride for 24 hr. gave a 60:40 mixture (by nmr integration) of α- (2) and β-himachalene (3) in 80% yield. A more efficient procedure for selective production of α-himachalene (2) employed a slight excess of phosphoryl chloride in refluxing pyridine for 1 hr. The resulting mixture of hydrocarbons obtained in 93% yield contained α- (2) and β-himachalene (3) in a ratio of 75:25 by nmr integration. Separation of the two isomeric hydrocarbons by flash chromatography[36] gave samples of pure α-himachalene (2) and β-himachalene (3) which were identical with the naturally occurring compounds by comparison of their nmr, ir and mass spectra with published values[5,6]. The effective overall yield of the mixture of α- and β-himachalenes was 22% over 12 steps from enone 37 as outlined in Scheme I.



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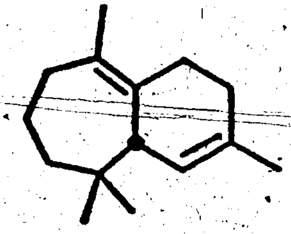
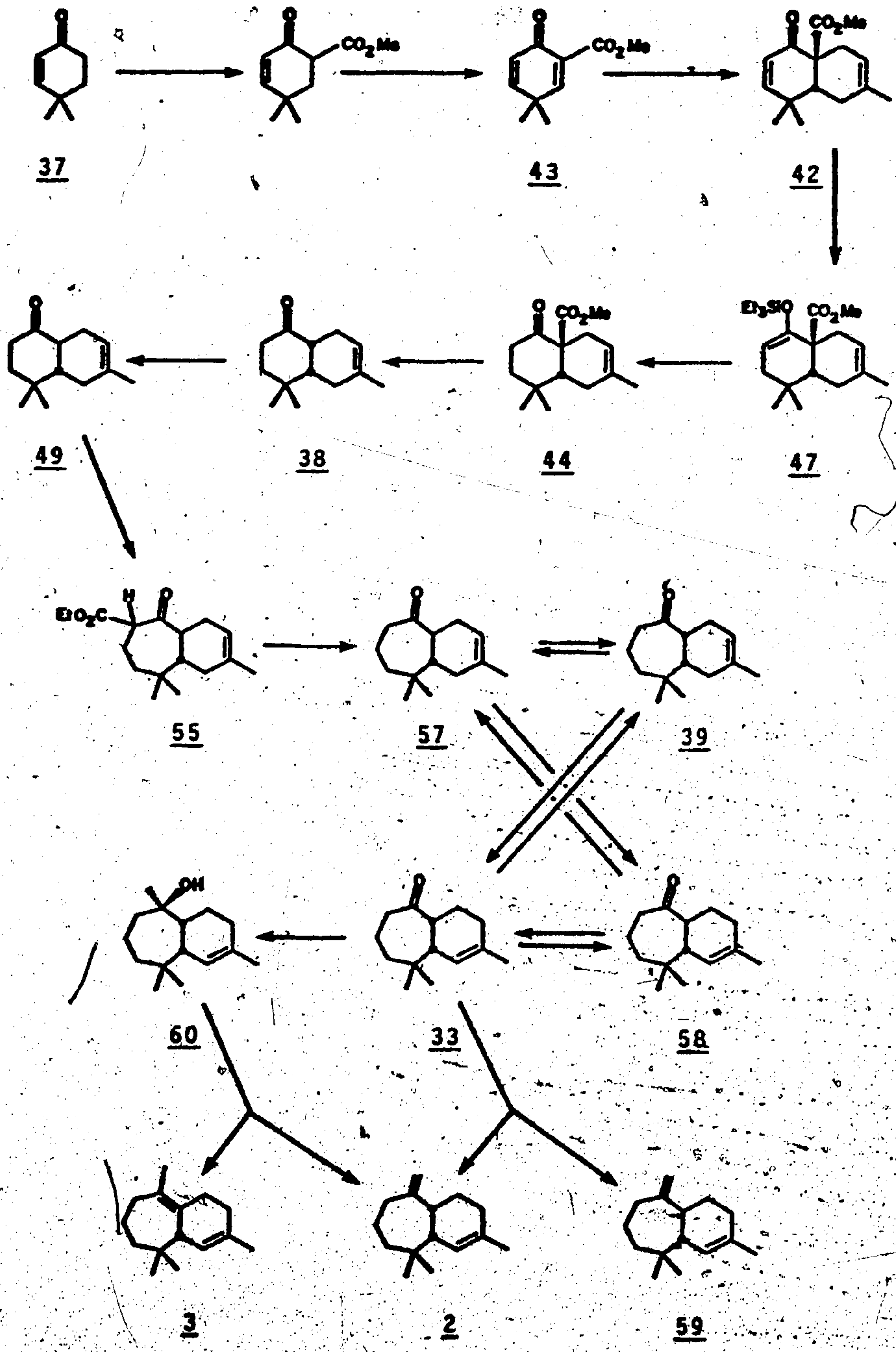


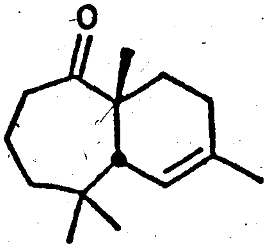
3

Synthetic Studies on Isohimachalone

For the proposed synthesis of *cis*-ketone 15 (isohimachalone) the saturated keto-ester 44, obtained by hydrosilylation/hydrolysis of keto-ester 42, was used as the key intermediate. Conversion of the carbomethoxyl group of 44 to an angular methyl required protection of the ketone prior to the reduction step. Thus ketone 44

Scheme I: -The Synthesis of α- and β-Himachalene





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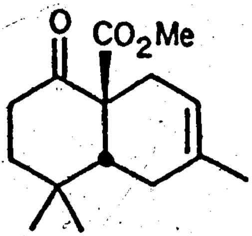
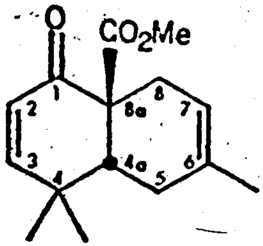


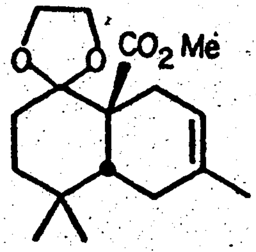
44



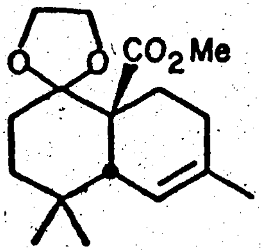
42

was treated with ethylene glycol and *p*-toluenesulfonic acid in refluxing benzene for 47 hr. and a ketal was obtained in 93% yield to which structure 61 was tentatively assigned.

To ascertain that the acidic ketalization conditions had not also caused migration of the double bond to give ketal 62, the ketal group



61

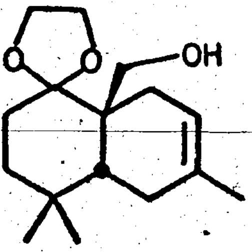


62

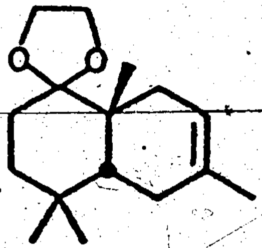
was removed by treatment with *p*-toluenesulfonic acid in acetone for 14 days. A single product was obtained in quantitative yield (based on recovery of 46% of the starting ketal) which was identical by nmr, ir and tlc analysis with the original keto-ester 44.

The production of un-isomerized keto-ester 44 from the very mild transketalization conditions indicated that the ketalization of 44 had occurred without migration of the double bond and that 61 was the structure of the product obtained.

Conversion of the carbomethoxyl group of 61 to a methyl group required reduction of the ester to the alcohol 63, followed by attachment of a leaving group and further reduction to give the methyl derivative 64. The ester 61 was easily reduced with lithium



63

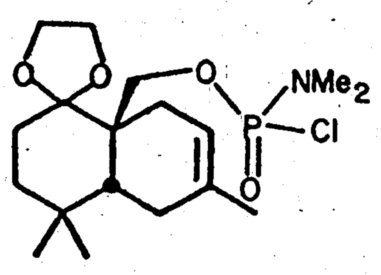


64

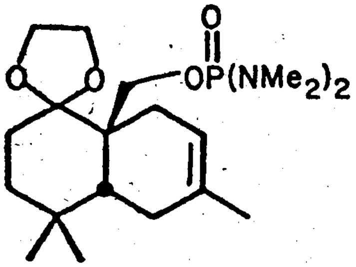
aluminum hydride in ether to give alcohol 63 in 92% yield. The alcohol 63 gave a molecular ion at m/e 266.1886 ($C_{16}H_{26}O_3$) in the mass spectrum and showed a sharp hydroxyl absorption at 3546 cm^{-1} in the ir spectrum. The nmr spectrum showed a vinyl proton as a broad singlet at δ5.14. The ketal group appeared as a four proton singlet at δ3.95 while the two protons of the hydroxyl substituted methylene group appeared as doublets of doublets at δ3.51 and 3.10 and the hydroxyl proton showed as a doublet of doublets at δ2.42. Methyl groups also appeared at δ1.62, 0.97 and 0.83.

The further reduction of the hydroxymethylene group of 63 to an angular methyl required the use of a derivative which could be reduced without steric interference from the adjacent neopentyl center. It has been shown[32] that tetramethyl phosphorodiamidate[37] (TMPDA) derivatives of alcohols can be reduced to hydrocarbons with lithium in ethylamine/tetrahydrofuran/*t*-butanol. Such TMPDA derivatives of stericly hindered alcohols are, however, difficult to prepare directly from reaction of the alcohol with tetramethyl phosphorodiamidic chloride. This difficulty can be circumvented[38] by conversion of the alcohol first to the dimethyl chlorophosphoramidate derivative using dimethylphosphoramidic dichloride followed by treatment of the resulting intermediate with dimethylamine to give the TMPDA derivative. Accordingly alcohol 63 was converted to the corresponding alkoxy anion by treatment with *n*-butyllithium in 1,2-dimethoxyethane/tetramethylethylenediamine (80:20) at 0° for 15 min. The anion was treated *in situ* with dimethylphosphoramidic dichloride[39] at room temperature for 23 hr. to give complete conversion to the intermediate 65. This compound was not isolated but was rapidly converted by the addition of excess liquid dimethylamine to the solution at 0°, into the TMPDA derivative 69 in 84% overall yield from alcohol 63.

Reduction of the TMPDA derivative 66 with lithium in ethylamine/tetrahydrofuran/*t*-butanol gave three principal products. One product,

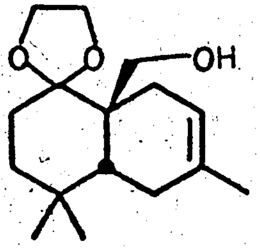


65

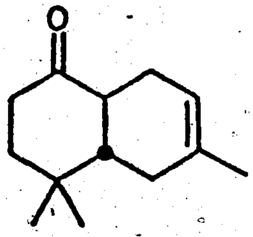


66

obtained in 14% yield, was found to be identical with the alcohol 65 and clearly resulted from cleavage of the P-O bond rather than C-O cleavage. The minor product, obtained in 5% yield, was found to be identical with the *trans*-ketone 49 obtained previously (*vide infra*).

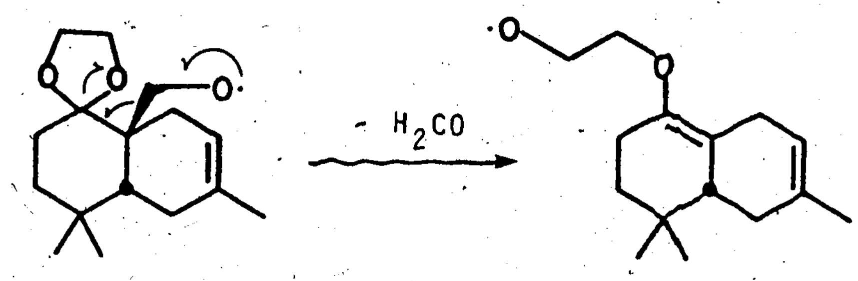


63



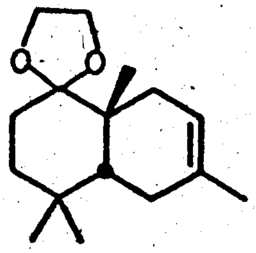
49

Possibly this ketone could occur via a 1,3-glycol-type cleavage in the radical which would result from P-O bond fission in the TMPDA derivative 66 as shown below. The major product, obtained in 69% yield was identified as the desired ketal 64. The exact mass of the molecular ion in the mass spectrum (m/e 250.1930) indicated

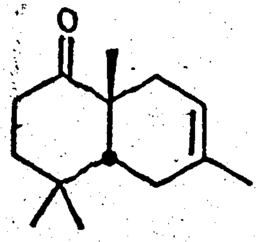


the chemical formula $C_{16}H_{26}O_2$. The nmr spectrum showed a vinyl ~~proton at δ5.22, a ketal group as a four proton singlet at δ3.86~~ and four methyl singlets at δ1.62, 0.88, 0.83 and 0.76.

Transketalization of ketal 64 with acetone in the presence of *p*-toluenesulfonic acid rapidly (2.5 hr.) gave a product identifiable as *cis*-ketone 45 in 97% yield. The compound gave a molecular ion



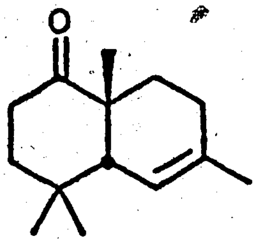
64



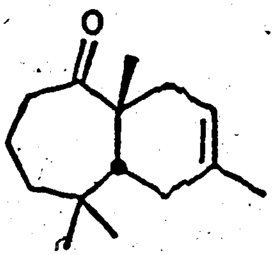
45

at m/e 206.1671 in the mass spectrum indicating the molecular formula $C_{14}H_{22}O$. The ir spectrum showed an absorption due to a saturated ketone in a six-membered ring at 1706 cm^{-1}. The nmr spectrum showed a vinyl proton as a multiplet at δ5.27 and four methyl groups as singlets at δ1.67, 1.02 and 0.95 (six protons).

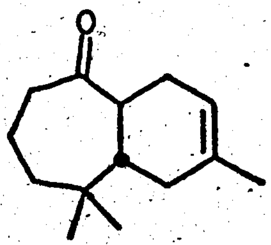
The synthesis of <u>15</u> could proceed from ketone <u>45</u> by two different routes: isomerization of the double bond (<u>67</u>) followed by homologation of the ketone ring, or homologation first (<u>68</u>) and then isomerization of the double bond. The isomerization of <u>68</u> to <u>15</u> has precedent in the acid catalysed isomerization of <u>57</u> to <u>58</u> in which the equilibrium ratio of the two compounds was approximately 33:67 (*vide supra*). On the other hand, examination of Dreiding models of <u>45</u> and <u>67</u> showed that in <u>45</u> the B ring could not achieve a stable



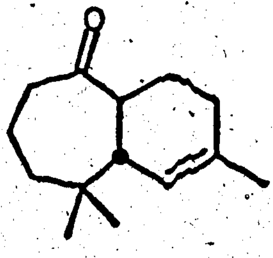
<u>67</u>



<u>68</u>



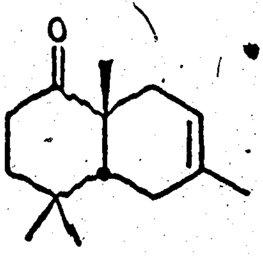
<u>57</u>



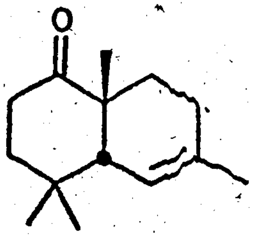
<u>58</u>

quasi-chair conformation without exerting considerable torsional strain on the C-4a/C-8a bond. In ketone 67 however, the quasi-chair conformation of the B ring could be attained without undue torsional strain. Ketone 67 therefore might be expected to predominate in an equilibrium mixture of 45 and 67.

Treatment of 45 with *p*-toluenesulfonic acid in refluxing benzene for 2 hr. gave an 85:15 equilibrium mixture of two inseparable compounds in 89% yield. The minor component was identified as ketone 45 by its gc retention time and by comparison of the minor signals in the nmr spectrum of the mixture with the spectrum of pure 45. The major component showed nmr signals at δ5.40 (multiplet) due to a vinyl proton and at δ1.71, 1.04, 0.97 and 0.94 (singlets) due to methyl groups. The structure 67 was tentatively assigned and this



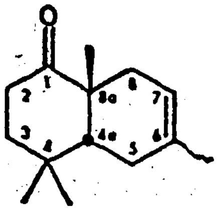
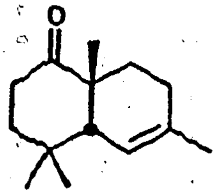
45



67

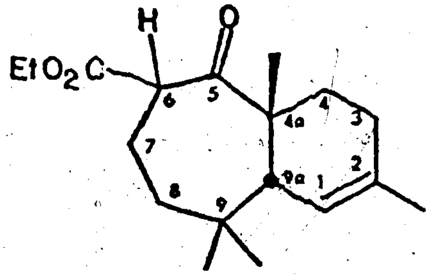
was confirmed by comparison of the cmr spectra (Table III) of 45 and 67. In both cases the signal due to C-4a appeared as the only high field doublet in the off resonance decoupled spectrum. In 45 the signal appeared at δ48.9 whereas in 67 the signal appeared at δ52.3

TABLE III. CMR Spectra (δ) of Ketones 45 and 67

	 45	 67
C-1	216.2	217.3
C-2	34.9	35.1
C-3	40.7	38.5
C-4	33.9	34.0
C-4a	48.9	52.3
C-5	28.0	120.5
C-6	132.1	133.7
C-7	117.7	26.2
C-8	33.7	29.3
C-8a	46.4	46.0
CH_3	32.2	31.5
	23.6	23.8
	23.2	23.1
	21.0	22.8

because of deshielding by the closer proximity of the double bond. As well, the olefinic carbon C-5 in 67 was deshielded (δ120.5) relative to C-7 of 45 (δ117.7) by the β-effect[40] caused by C-4.

As was stated for the synthesis of himachalenes (*vide supra*), the ring expansion of ketones such as 67 with ethyl diazoacetate[32] was expected[33,34] to proceed with predominant migration of the less substituted α-carbon to give β-keto esters such as 69. Treatment of



69

67* with ethyl diazoacetate and boron trifluoride etherate in ether for seven days gave two products (60:40) in a combined yield of 41% which were separated by column chromatography. The major product showed a molecular ion at m/e 292.2031 in the mass spectrum indicating the chemical formula $C_{18}H_{28}O_3$. The ir spectrum showed a band at 1748 cm^{-1} due to a saturated ester and another at 1706 due to a ketone in a seven membered ring. The nmr spectrum showed a vinyl proton as a doublet at δ5.32, and an ethyl group as a pair of

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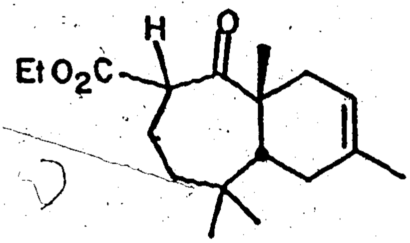
*The sample was contaminated with ~15%±5% of the isomeric ketone 45.

quartets (one proton each) at δ4.09 and 4.08 and a triplet at δ1.21. Methyl groups appeared as singlets at δ1.09, 0.97 and 0.67. A signal at δ3.92 was assigned to a proton on the α-carbon of a β-keto ester. The signal was a doublet of doublets with coupling constants of 12 and 4 Hz indicating that two protons were adjacent. The preceeding data, especially the coupling patterns of the vinyl and keto-ester protons indicated that the structure of this product was 69.

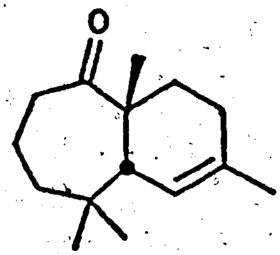
The minor product of the ring expansion reaction was later conclusively identified as 70 by comparison with an authentic sample



70

obtained from ketone 45. The presence of 70 among the reaction products probably stemed from the ring expansion of 45 which was present as an impurity (∿15%) in the starting material.

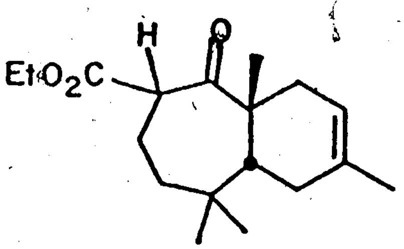
The decarboxylation of keto-ester 69 with lithium iodide dihydrate[31] proceeded to give a ketone in 10% yield. The product showed a molecular ion at m/e 220.1823 in the mass spectrum and showed a band at 1699 cm^{-1} in the ir spectrum indicating a ketone in a seven membered ring. The nmr spectrum showed a vinyl proton as a doublet at δ5.34 with a coupling constant of 4 Hz. Methyl groups appeared as singlets at δ1.69, 1.01, 0.97 and 0.69. The appearance of the vinyl proton as a doublet strongly suggested that this product had structure 15. The relatively poor yield obtained for conversion of 67 to 15 prompted investigation of the alternate route to 15 via ring expansion of ketone 45.



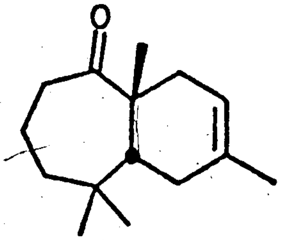
15

Treatment of 45 with ethyl diazoacetate and boron trifluoride etherate in ether for 48 hr. gave a single product (18 lines in the cmr spectrum) in 82% yield. The mass spectrum showed a molecular ion at m/e 292.2037, characteristic of the chemical formula $C_{18}H_{28}O_3$. The ir spectrum showed a band due to a saturated ester at 1750 cm^{-1} and one due to a seven-membered ring ketone at 1700 cm^{-1}. The nmr spectrum showed a vinyl proton as a broad singlet at δ5.34 and an ethyl group as a pair of quartets (one proton each) at δ4.11 and 4.09 and a triplet at δ1.22. Methyl groups appeared as singlets at δ1.66, 1.09, 0.98 and 0.71. A signal at δ3.86 was assigned to a proton at the α-carbon of a β-keto ester and appeared as a doublet of doublets with two coupling constants of 10 Hz each, indicating that there were two protons adjacent to it. The preceeding spectral data indicated that the structure of the ring expansion product was 70.

Decarboxylation of 70 with lithium iodide dihydrate[31] gave the corresponding ketone 68 in 86% yield. The ketone 68 showed a molecular ion at m/e 220.1829 ($C_{15}H_{24}O$) and an ir absorption at 1701 cm^{-1} indicating a ketone in a seven-membered ring. The nmr spectrum showed a vinyl proton as a broad singlet at δ5.30 and methyl singlets at δ1.63, 0.97, 0.95 and 0.69.

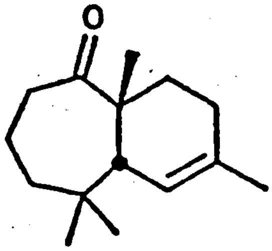


70



68

The attempted acid catalysed isomerization of 68 to 15 with oxalic acid in aqueous dioxan at reflux for 12 hr. gave only recovered starting material (89%). However, treatment of 68 with *p*-toluenesulfonic acid hydrate in refluxing benzene for 2 hr. produced two isomeric ketones in addition to a 5% recovery of starting material. The major product, obtained in 53% yield was identical with the ketone 15 produced by decarboxylation of keto-ester 70. The second product, obtained in 15% yield, gave a molecular ion at m/e 220.1831 in the mass spectrum. The ir spectrum showed a band at 1699 cm^{-1} due to a seven-membered ring ketone. The nmr spectrum



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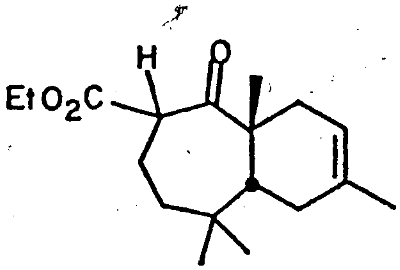
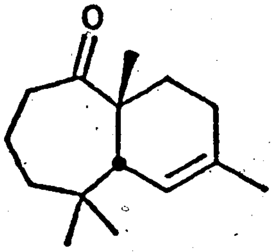


70

showed a vinyl proton as a multiplet at δ5.17 and methyl groups as singlets at δ1.60, 1.26, 0.94 and 0.75. Although the spectral data indicated that this compound was very closely related to ketones 15 and 68, the structure could not be assigned with certainty and it is referred to in this thesis as ketone A*.

Conclusive evidence in support of the assignment of the double bond position in ketones 15 and 68 was obtained from their cmr spectra (Table IV). In 15, C-9a appeared as the only high field doublet at



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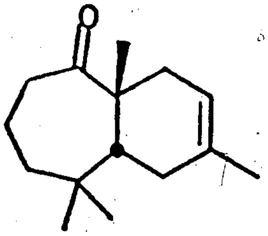

68

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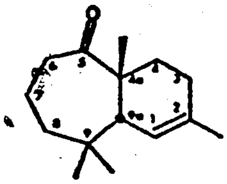
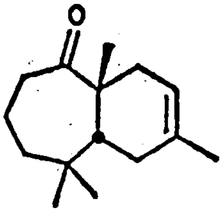
*Continued heating of the acidic reaction mixture for 22 hr. gave ketone A as the major product.

TABLE IV. CMR Spectra (δ) of Ketones 15 and 68

	 15	 68
C-1	50.2	45.0
C-2	121.8	18.1
C-3	134.1	132.1
C-4	27.1[a]	119.7
C-5	23.4	29.5[a]
C-6	49.7	49.1
C-7	218.0	217.8
C-8	40.5	35.4
C-9	b,a	30.1[a]
C-10	46.2	38.2
C-11	39.6	37.5
CH_3	33.4	29.6
	26.0	26.6
	24.5	26.1
	23.4	23.1

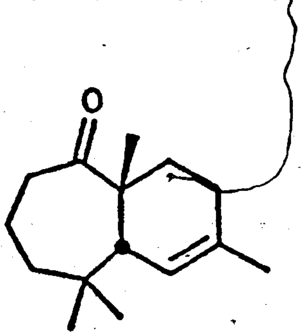
[a] This signal cannot be assigned with certainty.

[b] This signal is probably obscured by the signal of the cyclohexane standard (δ27.7).

δ50.2, deshielded relative to C-9a of 68 (δ45.0) by the adjacent double bond. Also the olefinic carbon C-1 of 15 (δ121.8) was deshielded relative to C-3 of 68 (δ119.7) due to a β-effect from the adjacent C-9.

With the placement of the double bond in 15 and 68 clearly defined by the spectroscopic evidence, and with the *cis* stereochemistry of the ring junction fixed by the structure of the key intermediate, Diels-Alder adduct 44, the assignment of structures 15 and 68 to their respective compounds was assured.

It is essential to note at this point that the spectral data (Table V) of neither ketone 15 nor 68, nor indeed of the unidentified ketone A, were identical with those reported by Dev[15] for naturally occurring isohimachalone. Examination of the data in Table V further indicated that a very close similarity existed between the nmr spectra of Dev's[15] isohimachalone and Teisseire's[14] *trans*-ketone 14. This, together with the non-identity of our synthetic 15 with the naturally occurring compound, strongly suggested that the naturally occurring isohimachalone isolated by Dev[15] might be identical with


15

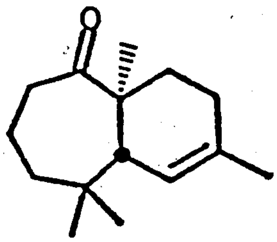

14

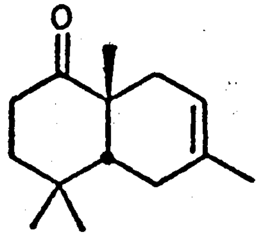
TABLE V. NMR Spectra (δ) of Several Isohimachalane Derivatives

Synthetic 15	Isohimachalone[15]	14[14]	68	Ketone A
5.44	5.50	5.53	5.30	5.17
2.56	2.60	2.55	2.84	
		2.00		
1.69	1.80	1.81	1.63	1.60
1.01	1.[illegible]3	1.12	0.97	1.26
0.97	0.98	0.90 (0.94)[a]	0.95	0.94
0.69	0.75	0.74	0.69	0.75

[a] Although the text of the paper refers to the chemical shift of this signal as δ0.90, the spectrum, which is illustrated in the paper, shows a shift at ∼δ0.94.

the *trans*-ketone 14 isolated by Teisseire[14]. Unfortunately, authentic samples of both naturally occurring ketones were no longer available[41,42] and so direct comparison of the compounds with each other and with 15 was not possible.

As was mentioned in the introduction, the synthesis of Teisseire's *trans*-ketone 14 could concieveably be approached via the *cis*-fused ketone 45. In a suitably activated derivative of 45, epimerization of the ring junction proton could lead ultimately to the *trans*-fused product 71. This transformation might be achieved by selective oxidation of the allylic C-5 methylene group of ketal 64 to give the ketone 72. Base catalysed epimerization of the resulting ketone to give *trans*-ketone 73 followed by reduction of the carbonyl of 73 to a methylene group could give *trans*-ketal 74. This ketal could then be converted to the *trans*-ketone 14 by a route analagous to that used for conversion of ketal 64 to *cis*-ketone 15.



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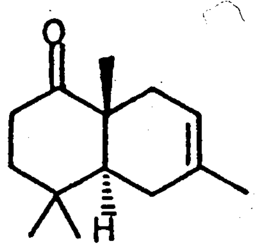

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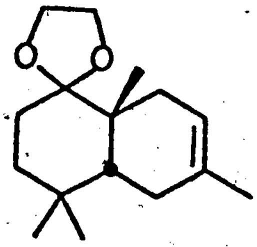

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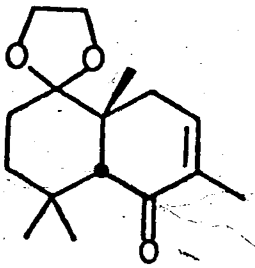

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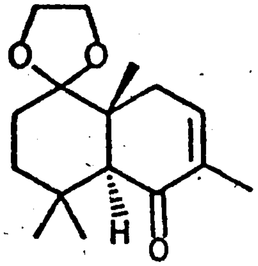

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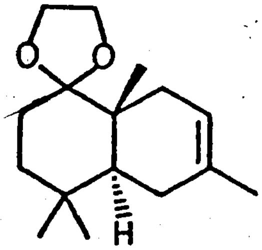
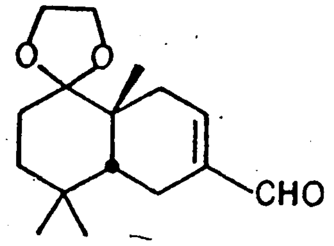


74

Treatment of ketal 64 with selenium dioxide[43] in refluxing *t*-butanol gave a complex mixture of products which were separated by column chromatography. Four principal products were obtained and identified by spectroscopic analysis as aldehydes 75 (34% yield) and 76 (18% yield) as well as alcohols 77 (32% yield) and 78 (16% yield). No detectable quantity of the desired C-5 oxidation product was observed.

The observed oxidation of ketal 64 predominantly at the allylic methyl group under these conditions indicated that a more suitable



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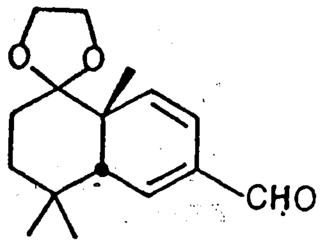

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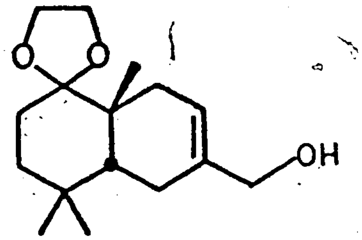

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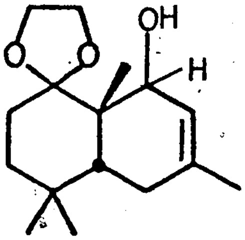

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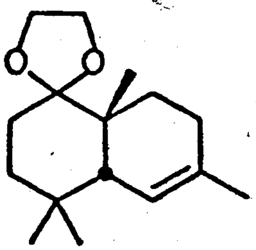
starting material would be the ketal 79. Preferential oxidation of the allylic methyl group would lead to aldehyde 80 in which the



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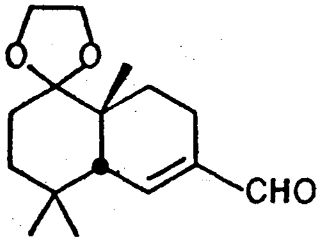

80

ring junction proton should be epimerizable under basic conditions. Ketal 79 was easily prepared by treatment of ketone 67[*], obtained by isomerization of ketone 45, with ethylene glycol and *p*-toluenesulfonic acid in refluxing benzene. The product, obtained in 99% yield was a mixture of two compounds in an 85:15 ratio. The minor component was shown by comparison of nmr spectra to be identical with pure ketal 64[**] and clearly arose from ketalization of the ketone 45 which was present as an impurity in the starting material. The major component was obtained pure by recrystallization of the product mixture and showed a molecular ion at m/e 250.1929 in the mass spectrum indicating the molecular formula $C_{16}H_{26}O_2$. The ir spectrum showed the presence of a trisubstituted double bond with a band at 812 cm^{-1}. The nmr spectrum showed a vinyl proton as a broad doublet (J = 5 Hz) at δ5.37. The ketal group appeared as a complex four proton signal centered at δ4.86. Methyl groups appeared as singlets at δ1.70, 0.97, 0.84 and 0.79.

In a more efficient overall conversion of ketone 45 to ketal 79, crude 45 was treated with *p*-toluenesulfonic acid in refluxing benzene for 2 hr. Then ethylene glycol was added and the heating

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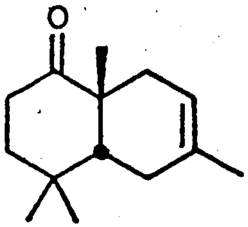
[*] This material was contaminated with ~15% of the isomeric ketone 45.

[**] This material could be recycled into the synthesis by deketalization and acid catalysed isomerization to give ketone 67.

continued with separation of water for a further 21 hr. The resulting 85:15 mixture of ketals 79 and 64 was subsequently isolated in 98% overall yield from ketone 45.



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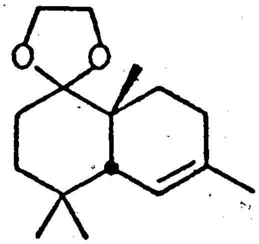
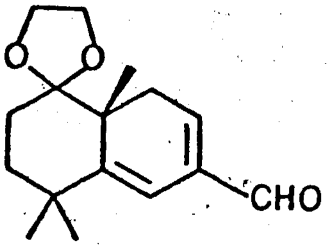
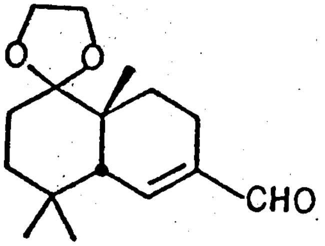


79

Selenium dioxide oxidation of ketal 79 in refluxing *t*-butanol gave a complex mixture of products which were separated by column chromatography. Three principal products were obtained. One product, obtained in 18% yield, was identified as aldehyde 81. A second product, also obtained in 18% yield, showed a molecular ion at m/e 264.1724 in the mass spectrum indicating the chemical formula



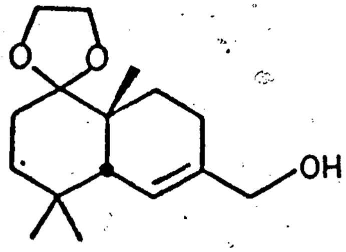
81



80

$C_{16}H_{24}O_3$. The ir spectrum showed aldehydic C-H absorptions at 2805 and 2710 cm^{-1} and an α,β-unsaturated aldehyde at 1686 cm^{-1}. The nmr spectrum showed an aldehydic proton as a singlet at δ9.42, a vinyl proton as a doublet of doublets of doublets (J = 5, J' = J" = ∿2 Hz) and a ketal group as a four proton multiplet at δ3.90. Methyl groups appeared as singlets at δ1.10, 0.85 and 0.78. These data were consistent with the assignment of structure 80.

The third product (12% yield) of selenium dioxide oxidation of ketal 79 showed a molecular ion at m/e 266.1890 ($C_{16}H_{26}O_3$) in the mass spectrum. The ir spectrum showed a hydroxyl absorption at 3438 cm^{-1}. The nmr spectrum showed a vinyl proton as a doublet (J = 6 Hz) at δ5.65. A complex signal at δ3.80 which integrated for seven protons was attributed to a ketal group and the three protons of a hydroxymethylene group. Methyl singlets appeared at δ0.98, 0.84 and 0.79. These data indicated the structure as alcohol 82.

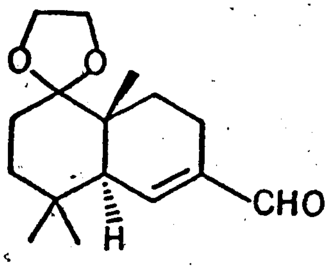


82

This alcohol was easily converted to aldehyde 80 in 52% yield by oxidation with pyridinium chlorochromate[44] in dichloromethane.

Treatment of aldehyde 80 with sodium hydroxide in aqueous methanol at room temperature for 19 hr. produced no detectable isomeric aldehyde and 85% of *cis*-aldehyde 80 was recovered. However, treatment of a similar reaction mixture at reflux for 22 hr. gave (69% yield) a 52:48 (gc analysis) equilibrium mixture of *cis*-aldehyde 80 (major) and a second compound (minor). Separation of the two components by flash chromatography[36] gave the minor component in pure form. The mass spectrum showed a molecular ion at m/e 264.1725 ($C_{16}H_{24}O_3$). The ir showed an aldehydic C-H absorption at 2710 cm^{-1} and an α,β-unsaturated aldehyde band at 1683 cm^{-1}. The nmr spectrum showed an aldehydic proton as a singlet at δ9.37 and a vinyl proton as a doublet of doublets of doublets ($J = J' = J'' = \sim 2$ Hz) at δ6.56. The ketal group appeared as a broad singlet (four protons) at δ3.85 and methyl groups gave singlets at δ1.01, 0.90 and 0.88. These data were consistent with the assignment of structure 83.

The stereochemistry of aldehydes 80 and 83 was shown conclusively by the coupling constants of the vinyl protons in their nmr spectra. In *cis*-aldehyde 80 the vinyl proton signal at δ6.68 was a doublet of doublets of doublets with one large coupling (5 Hz) to the proton at C-4a and two small long range couplings (2 Hz each) to the protons at C-7. In *trans*-aldehyde 83 this proton (δ6.56) was also a doublet of doublets of doublets however all three coupling constants were approximately 2 Hz. Examination of Drieding



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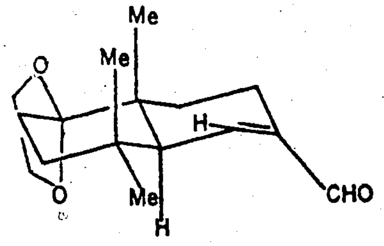
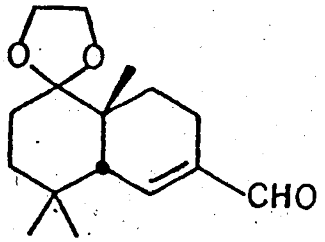


83a



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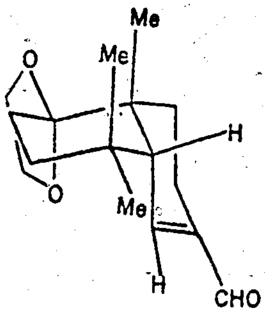
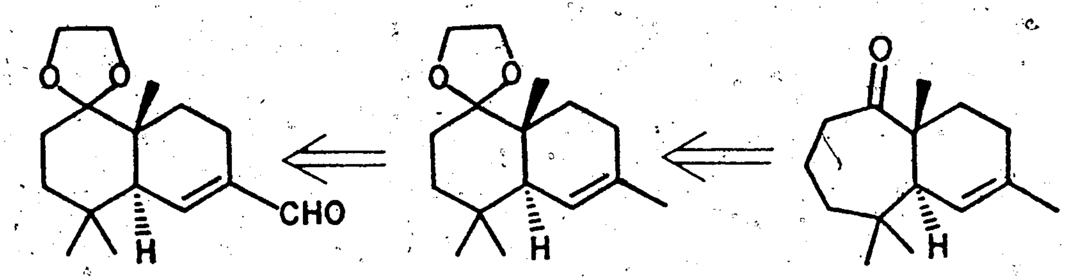


80a

models showed that, in the most stable conformation of *cis*-aldehyde 80a the dihedral angle between the C-4a and C-5 protons was ∿40° from which a coupling constant of ∿5 Hz would be expected[45]. On the other hand, in *trans*-aldehyde 83, the dihedral angle between these two protons was ∿90° which should produce a very small coupling between the two protons[45]. These predictions are in agreement with the observed couplings described above.

Methods are currently under study for the conversion of *trans*-aldehyde 83 to *trans*-ketal 84 which in principle could be converted to *trans*-ketone 14 by deketalization and ring expansion.



83 84 14

Experimental

General

For general remarks see Chapter 1 of this thesis. All gas chromatography (gc) was performed on a Hewlett-Packard 5750 research chromatograph using stainless steel columns (8 ft. × 1/8 in.) packed with 10% diethylene glycol succinate on 80-100 mesh Chromosorb-W, acid washed and treated with dimethylchlorosilane.

Materials

Benzene was distilled over lithium aluminum hydride. Pyridine was distilled over barium oxide and stored over potassium hydroxide pellets. Boron trifluoride etherate was distilled over calcium hydride according to the procedure of Brown[46,47]. Nitrogen was passed through a purification train of Fieser's solution[47], saturated aqueous lead acetate, concentrated sulfuric acid and potassium hydroxide pellets. Dienone-ester 43[48] was prepared in two steps from 4,4-dimethyl-2-cyclohexen-1-one[49] according to the procedure described in Chapter 1 of this thesis.

8aβ-Carbomethoxy-4,4,6-trimethyl-4aβ,5,8,8a-tetrahydro-1(4H)-naphthalenone (42)*

Dienone-ester 43 (1.03 g, 5.72 mmol) was dissolved in ether (freshly distilled over lithium aluminum hydride) under an atmosphere of nitrogen. Anhydrous stannic chloride (745 mg, 2.86 mmol) was added with stirring followed by addition of isoprene (11.4 ml, 114 mmol). After stirring for 84 hr., saturated aqueous sodium bicarbonate (10 ml) was added. The resulting mixture was extracted with ether and the extracts were washed with water, dried, filtered and concentrated. Column chromatography of the residue on silica gel, eluting with 8-20% ether in petroleum ether, gave a mixture of keto-ester 42 and its regiosomer 8aβ-carbomethoxy-4,4,7-trimethyl-4aβ,-5,8,8a-tetrahydro-1(4H)-naphthalenone (82:18 by gc analysis, 1.37 g, 97% yield) which crystallized on standing. As an alternative to chromatographic purification the crude residue could be purified by molecular distillation in a Kugelrohr apparatus (~120°C at 0.5 Torr.) to give a mixture of keto-ester 42 and its regioisomer in 99% yield. One recrystallization of this mixture from ether gave pure keto-ester 42 (872 mg) as colourless crystals. Spectral data for keto-ester 42 have been reported (Chapter 1). Additional keto-ester 42 could be

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*The stereochemical designations used in this and all other chemical names in this section denote relative stereochemistry. All compounds used and obtained were racemic.

obtained either by fractional crystallization from the mother liquor or by preparative high pressure liquid chromatography as described in Chapter 1 of this thesis.

8aβ-Carbomethoxy-1-triethylsilyloxy-4,4,6-trimethyl-3,4,4aβ,5,8,8a-hexahydronaphthalene 47

Finely divided keto-ester 42 (760 mg, 3.06 mmol) was suspended in triethylsilane (710 mg, 6.12 mmol) and *tris*-triphenylphosphine rhodium(I) chloride[28] (14 mg, 0.015 mmol) was added. The mixture was stirred for 5 hr. after which additional triethylsilane (710 mg) was added. After a further 19 hr. the mixture was diluted with petroleum ether, filtered, and concentrated to give crude silyl-enol ether 47 (1.28 g). Column chromatography of crude 47 on silica gel, eluting with 3-5% ether in petroleum ether, gave pure silyl enol ether 47 (1.01 g, 91% yield) as a colourless oil: nmr δ5.28 (m, 1H, $CH_3{-}\overset{|}{C}{=}C\underline{H}{-}$), 4.63 (dd, 1H, J = 6, J' = 3 Hz, ${-}O{-}\overset{|}{C}{=}C\underline{H}{-}$), 3.58 (s, 3H, ${-}O{-}CH_3$), 2.63 (dd, 1H, J = J' = 8 Hz, C-4a H), 1.62 (s, 3H, ${=}\overset{|}{C}{-}C\underline{H}_3$), 0.96 (s, 2X, 3H, ${-}\overset{|}{C}(CH_3)_2$), 0.96 (t, 9H, J = 7 Hz, $3X{-}CH_2{-}C\underline{H}_3$), and 0.61 (q, 6H, J = 7 Hz, $3X{-}C\underline{H}_2{-}CH_3$); ir 1743, 1728 (C=O), 1674 (enol C=C), 1387, 1378, 1366 (CH_3), and 820 cm^{-1} (C=CH); ms M^+ 364.2433 (calcd. for $C_{21}H_{36}O_3Si$: 364.2433). Anal. Calcd. for $C_{21}H_{36}O_3Si$: C 69.18, H 9.95; Found: C 69.36, H 9.95.

8aβ-Carbomethoxy-4,4,6-trimethyl-3,4,4aβ,5,8,8a-hexahydro-1(2*H*)-naphthalenone (44)

Pure silyl enol ether 47* (993 mg, 2.72 mmol) was dissolved in methanol (50 ml) and a solution of 10% aqueous potassium carbonate (10 ml) was added. The mixture was stirred for 4 hr. then poured into water and extracted with methylene chloride. The extracts were washed with water, dried, filtered and concentrated. Column chromatography of the residue on silica gel, eluting with 3-10% ether in petroleum ether, gave keto-ester 44** (598 mg, 88% yield) as a colourless oil: nmr δ5.28 (m, 1H, $=CH-$), 3.62 (s, 3H, $-O-CH_3$), 1.60 (s, 3H, $=\overset{|}{C}-CH_3$), 1.07 (s, 3H, CH_3) and 0.97 (s, 3H, CH_3); Cmr 209.0, 173.7, 131.9, 117.7, 59.5, 52.4, 44.9, 38.4, 35.6, 33.4, 30.7, 29.6, 28.6, 23.8, and 23.5; ir 1743, 1731 (C O, ester), 1710 (C=O, ketone), 1427 ($-CH_2-C=O$), 1388, 1367 (CH_3), and 783 cm^{-1} (C=CH); ms M^+ 250.1570 (calcd. for $C_{15}H_{22}O_3$: 250.1569). Anal. Calcd. for $C_{15}H_{22}O_3$: C 71.97, H 8.86; Found: C 71.83, H 8.73.

4,4,6-Trimethyl-3,4,4aβ,5,8,8aβ-hexahydro-1(2*H*)-naphthalenone (38) and 4,4,6-trimethyl-3,4,4aβ,5,8,8aα-hexahydro-1(2*H*)-naphthalenone (49)

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[*] Crude silyl enol ether 47 could be hydrolysed using the procedure above to give keto-ester in 94% overall yield from keto-ester 42.

[**] This material required a long period under vacuum (∿24 hr. at 0.5 Torr) to remove triethyl silyl hydroxide which was present as a contaminant.

Keto-ester 44 (966 mg, 3.86 mmol) was dissolved in 2,4,6-collidine (24 ml) under an atmosphere of nitrogen. Anhydrous lithium iodide (4.14 g, 30.9 mmol) was added to the stirred solution followed by addition of water (556 mg, 30.9 mmol). The mixture was heated under reflux for 2.5 hr. then cooled to room temperature, poured into cold 5% aqueous hydrochloric acid and extracted with ether. The extracts were washed with ice-cold 5% aqueous hydrochloric acid and water, dried, filtered and concentrated. Gc analysis of the residue showed the presence of *cis*- and *trans*-ketones 38 and 49 in a ratio of ∿10:90. Column chromatography of the residue on silica gel, eluting with 4% ether in petroleum ether, gave *trans*-ketone 49 (550 mg, 74% yield) which crystallized on standing. One recrystallization from ether gave colourless crystals of pure *trans*-ketone 49: mp 71-71.5°C; nmr δ5.33 (br s, 1H, $=CH-$), 1.61 (s, 3H, $=\overset{|}{C}-CH_3$), 1.07 (s, 3H, $-CH_3$), and 0.98 (s, 3H, $-CH_3$); Cmr δ212.8, 133.1, 120.2, 48.3, 46.0, 42.2, 38.9, 33.3, 32.5, 29.7, 26.3, 24.2, and 20.0; ir 1706 (C=O), 1387, 1380 and 1366 cm^{-1} (CH_3); ms M^+ 192.1513 (calcd. for $C_{13}H_{20}O$: 192.1514). Anal. Calcd. for $C_{13}H_{20}O$: C 81.20, H 10.48; Found: C 80.74, H 10.55. Further elution with 4-5% ether in petroleum ether gave a mixture of *cis*- and *trans*-ketones 38 and 49 (67:33 by gc analysis, 74 mg, 10% yield). Further elution with 5% ether in petroleum ether gave *cis*-ketone 38 (16 mg, 2% yield) which crystallized on standing. One recrystallization from ether gave pure *cis*-ketone 38: mp : 51-53°C; nmr 5.22 (br s, 1H, $=CH$), 2.81

(dd, 1H, J = J' = 5 Hz, $-\overset{|}{C}H-CO-$), 2.50 (dm, 1H, J = ∿18 Hz, C-8 Hb), 1.58 (s, 3H, $=\overset{|}{C}-CH_3$), 1.32 (s, 3H, $-CH_3$) and 0.98 (s, 3H, $-CH_3$); Cmr δ211.9, 131.4, 118.9, 46.6, 43.6, 37.9, 35.6, 33.0, 29.3, 27.8, 26.9, 24.1, and 23.7; ir 1709 (C=O), 1390 and 1370 cm^{-1} (CH_3); ms M^+ 192.1522 (calcd. for $C_{13}H_{20}O$: 192.1514). Anal. Calcd. for $C_{13}H_{20}O$: C 81.20, H 10.48; Found: C 80.87, H 10.44. The overall yield of ketones 38 and 50 was 86%*.

Equilibration of *cis*- and *trans*-Ketones 38 and 49

A mixture of *cis*- and *trans*-ketones 38 and 49 (50:50 by gc analysis, 618 mg, 3.21 mmol) was dissolved in methanol (25 ml) and 1.0 N aqueous sodium hydroxide (5 ml) was added.. After stirring for 1 hr. the mixture was extracted with methylene chloride. The extracts were washed with water, dried, filtered and concentrated. GC analysis of the residue showed the presence of *cis*- and *trans*-ketones 38 and 49 in a ratio of 18:82. Column chromatography of the residue on silica gel, eluting with 3% ether in petroleum ether, gave pure *trans*-ketone 49 (401 mg, 65% yield). Continued elution gave a mixture of *cis*- and *trans*-ketones 38 and 49 (50:50 by gc analysis, 160 mg, 26% yield). Further elution with 3-5%

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*On one occasion, using 4.0 equivalents of lithium iodide dihydrate reagent and heating for 5 hr., a total yield of 94% (based on consumption of 71% of the starting material) of *cis*- and *trans*-ketones 38 and 49 (in a ratio of 20:80 by gc analysis) was obtained.

ether in petroleum ether, gave pure *cis*-ketone 38 (27 mg, 4% yield). The total recovery of ketones 38 and 49 was 95%.

6-Carboethoxy-3,9,9-trimethyl-1,4,4aβ,6,7,8,9,9aβ-octahydro-(5H)-benzocyclohepten-5-one (51) and 5-Carboethoxy-1,4,4aβ,6,7,8,9,9aβ-octahydro-(5H)-benzocyclohepten-6-one(52)

Ketone 50 (100 mg, 0.52 mmol) was dissolved in anhydrous ether (2 ml) under a nitrogen atmosphere in a flask wrapped in aluminum foil to exclude light. Boron trifluoride etherate (148 mg, 1.04 mmol) was added followed after 15 min. by ethyl diazoacetate (119 mg, 1.04 mmol). After 24 hr. additional boron trifluoride etherate (148 mg, 1.04 mmol) and ethyldiazoacetate (119 mg, 1.04 mmol) were added. After a further 48 hr. the reaction mixture was cooled to 0° and saturated aqueous sodium bicarbonate (10 ml) was added. The resulting mixture was extracted with ether, and the extracts were washed with water, dried (sodium sulfate) filtered and concentrated. Column chromatography of the residue on silica gel, eluting with 5% ether in Skelly B, gave keto-ester 51 (17 mg, 12% yield): nmr δ5.20 (m, 1H, $=\underline{\text{C}}\text{H}-$), 4.08 (q, 2H, J = 7 Hz, $-\text{O}-\text{C}\underline{\text{H}}_2-\text{CH}_3$), 3.10 (dd, 1H, J = 10, J' = 5 Hz, $-\text{CO}-\overset{|}{\text{C}}\text{H}-\text{CO}_2-$), 1.66 (s, 3H, $=\overset{|}{\text{C}}-\text{CH}_3$), 1.26 (t, 3H, J = 7 Hz, $-\text{O}-\text{CH}_2-\text{C}\underline{\text{H}}_3$), 1.18 (s, 3H, $-\text{CH}_3$), and 0.97 (s, 3H, $-\text{CH}_3$); ir (neat) 1738 (ester C=O), 1702 (ketone C=O), 1391 and 1370 cm^{-1} (CH$_3$); ms M$^+$ 278. Continued elution gave a 50:50

mixture of keto-esters 51 and 52 (28 mg, 19% yield). Continued elution gave keto-ester 52 (12 mg, 8% yield): nmr δ5.37 (m, 1H, $=CH-$), 4.10 (q, 2H, J = 7 Hz, $-O-\underline{CH_2}-CH_3$), 3.25 (d, 1H, J = 10 Hz, $-CO-\overset{|}{C}H-CO_2-$), 1.64 (s, 3H, $=\overset{|}{C}-CH_3$), 1.26 (t, 3H, J = 7 Hz, $-O-CH_2-\underline{CH_3}$), 1.20 (s, 3H, $-CH_3$), and 0.95 (s, 3H, $-CH_3$); ir (neat) 1742 (ester C=O), 1706 (ketone C=O), 1393 and 1370 cm^{-1} (CH$_3$).

6-Carboethoxy-3,9,9-trimethyl-1,4,4aα,6,7,8,9,9aβ-octahydro-(5H)-benzocyclohepten-5-one (53) and 5-carboethoxy-3,9,9-trimethyl-1,4,4aα,6,7,8,9,9aβ-octahydro-(5H)-benzocyclohepten-6-one (54)

Ketone 48 (361 mg, 1.88 mmol) was dissolved in anhydrous ether (5 ml) under a nitrogen atmosphere and cooled to 0°. Boron trifluoride etherate (355 mg, 2.5 mmol) was added followed after 15 min. by ethyl diazoacetate (252 mg, 2.2 mmol). After 4 hr. additional boron trifluoride etherate (355 mg, 2.5 mmol) and ethyl diazoacetate (320 mg, 2.8 mmol) were added. After stirring for an additional 90 min. saturated aqueous sodium bicarbonate (5 ml) was added and the resulting mixture was extracted with chloroform. The extracts were washed with water, dried (sodium sulfate), filtered and concentrated. Column chromatography of the residue on silica gel, eluting with 5% ether in Skelly B, gave keto-ester 53 (272 mg, 53% yield) which crystallyzed on standing: mp 40-49°; nmr δ5.33 (m, 1H, $=CH-$), 4.10 (q, 2H, J = 7 Hz, $O-\underline{CH_2}-CH_3$), 3.57 (dd, 1H,

$J = 11$, $J' = 3$ Hz, $-\text{CO}-\overset{|}{\text{C}}\text{H}-\text{CO}_2-$), 1.67 (s, 3H, $=\overset{|}{\text{C}}-\text{CH}_3$), 1.22 (t, 3H, $J = 7$ Hz, $-\text{O}-\text{CH}_2-\text{C}\underline{\text{H}}_3$), 0.92 (s, 3H, $-\text{CH}_3$), and 0.73 (s, 3H, $-\text{CH}_3$); Cmr δ210.6, 170.3, 131.6, 121.4, 60.9, 54.4, 53.8, 44.1, 42.9, 35.8, 34.7, 30.5, 27.2, 24.5, 22.7, 19.3, and 14.1; ir (neat) 1748 (ester C=O), 1702 (ketone C=O), 1392 and 1371 cm^{-1} (CH_3); ms M^+ 278.1873 (calcd. for $C_{17}H_{26}O_3$: 278.1881). Continued elution gave a mixture of keto-esters 53 and 54 (83:17 by nmr integration, 107 mg, 27% yield). Continued elution gave keto-ester 54 (22 mg, 5% yield): nmr (CDCl_3) δ5.38 (m, 1H, $=\text{C}\underline{\text{H}}-$), 4.21 (q, 2H, $J = 7$ Hz, $-\text{O}-\text{C}\underline{\text{H}}_2-\text{CH}_3$); 3.55 (d, 1H, $J = 9$ Hz, $-\text{CO}-\overset{|}{\text{C}}\text{H}-\text{CO}_2-$), 1.64 (s, 3H, $=\overset{|}{\text{C}}-\text{CH}_3$), 1.28 (t, 3H, $J = 7$ Hz, $-\text{O}-\text{CH}_2-\text{C}\underline{\text{H}}_3$), 1.02 (s, 3H, $-\text{CH}_3$), and 0.79 (s, 3H, $-\text{CH}_3$); ir (neat) 1743 (ester C=O), 1705 (ketone C=O), 1390, 1368 (CH_3), and 795 cm^{-1} (CH_3).

6-Carboethoxy-2,9,9-trimethyl-1,4,4aα,6,7,8,9,9aβ-octahydro-(5H)-benzocyclohepten-5-one (55) and 5-carboethoxy-2,9,9-trimethyl-1,4,4aα,6,7,8,9,9aβ-octahydro-(5H)-benzocyclohepten-6-one (56)

Ketone 49 (1.69 g, 8.78 mmol) was dissolved in anhydrous ether (25 ml) under an atmosphere of nitrogen in a flask wrapped in aluminum foil to exclude light. The solution was cooled to 0° and boron trifluoride etherate (2.49 g, 17.6 mmol) was added with stirring. Then ethyl diazoacetate (2.00 g, 17.6 mmol) was added. After 1 hr. saturated aqueous sodium bicarbonate (5 ml) was added slowly (5 min.) and the resulting mixture was extracted with methylene chloride. The extracts were washed with water, dried, filtered and concentrated. Column chromatography of the residue on silica gel, eluting with 5% ether in petroleum ether, gave keto-ester 55 (2.09 g, 86% yield*) as a pale yellow oil: nmr δ5.33 (br. s, 1H, $=CH-$), 4.08, 4.06 (each q, total 2H, each J = 8 Hz, $-O-C\underline{H}_2-CH_3$), 3.53 (dd, 1H, J = 10, J' = 4 Hz, $-CO-\overset{|}{C}H-CO_2-$), 1.65 (s, 3H, $=\overset{|}{C}-CH_3$), 1.21 (dd, 3H, J = J' = 8 Hz, $-O-CH_2-C\underline{H}_3$), 0.95 (s, 3H, $-CH_3$), and 0.76 (s, 3H, $-CH_3$); Cmr δ211.0, 170.3, 134.4, 118.4, 60.9, 54.0, 53.4, 44.1, 43.0, 35.8, 32.0, 30.4 (two carbons), 24.4, 23.5, 19.2, and 14.1; ir 1746 (ester C=O), 1703 (ketone C=O), 1390 and 1368 cm^{-1} (CH_3); ms M^+ 278.1883 (calcd. for $C_{17}H_{26}O_3$: 278.1881). Anal. Calcd. for $C_{17}H_{26}O_3$: C 73.35, H 9.41; Found: C 73.45, H 9.69. Continued elution gave a mixture of keto-esters 55 and 56 (50:50 by nmr integration, 154 mg, 6% yield*). Further elution with 5-30% ether in petroleum ether gave keto-ester 56 (195 mg, 8% yield*) which crystallized on standing. One recrystallization from ether gave pure white crystals of keto-ester 56: mp 92-96°C; nmr 5.27 (br s, 1H, $=CH-$), 4.10 (q, 2H, J = 8 Hz, $-O-C\underline{H}_2-CH_3$), 3.28 (d, 1H, J = 8 Hz, $-CO-\overset{|}{C}H-CO_2-$), 2.45 (m, 2H, $-CH_2-CO-$), 1.63 (s, 3H, $=\overset{|}{C}-CH_3$), 1.25 (t, 3H, J = 8 Hz, $-O-CH_2-C\underline{H}_3$), 1.02 (s, 3H, $-CH_3$), and 0.81 (s,

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*This material required a long period under vacuum (~24 hr. at 0.5 Torr) to remove ethyl glycolate, a product of decomposition of ethyl diazoacetate.

3H, $-CH_3$); Cmr δ207.5, 169.4, 134.1, 119.3, 63.6, 61.0, 49.8, 40.5, 36.7 (two carbons), 35.9, 33.6, 32.9, 31.7, 23.0, 19.5, and 14.1; ir 1750 (ester C=O), 1706 (ketone C=O), 1392, 1369 (CH_3), and 783 cm^{-1} (C=CH); ms M^+ 278.1886 (calcd. for $C_{17}H_{26}O_3$: 278.1882). Anal. Calcd. for $C_{17}H_{26}O_3$: C 73.35, H 9.41; Found: C 73.18, H 9.43. The overall yield of keto-esters 55 and 56 was 100% and in a ratio of ∿90:10 by weight.

Lithium Iodide Dihydrate-Collidine Reagent

Finely divided anhydrous lithium iodide (514 mg, 3.84 mmol) was suspended in 2,4,6-collidine (3.05 ml) with vigorous stirring. Water (138 μl, 7.68 mmol) was added and the suspension rapidly dissolved. The resulting pale yellow solution had a calculated concentration of 1.28 N in lithium iodide dihydrate.

2,9,9-Trimethyl-1,4,4aα,6,7,8,9,9aβ-octahydro-(5H)-benzocyclohepten-5-one (57)

Keto-ester 55 (307 mg, 1.10 mmol) was dissolved in lithium iodide dihydrate-collidine reagent (5.00 ml, 6.60 mmol) under an atmosphere of nitrogen. The resulting mixture was heated at reflux with stirring for 1 hr. then cooled to room temperature, poured into cold 5% aqueous hydrochloric acid and extracted with ether. The extracts were washed with ice-cold aqueous hydrochloric acid and water, dried, filtered and concentrated. Column chromatography of the residue on silica gel, eluting with 3-5% ether in petroleum ether, gave ketone 57 (192 mg, 85% yield[*]) which crystallized on standing. One recrystallization from ether gave colourless crystals of pure ketone 57: mp 53-54°C; nmr 5.32 (br s, 1H, $=\text{CH}-$), 2.52 (ddd, 1H, J = J' = 10, J" = 3 Hz, $-\text{CO}-\overset{|}{\text{C}}\text{H}-$), 1.64 (br s, 3H, $=\overset{|}{\text{C}}-\text{CH}_3$), 0.95 (s, 3H, $-\text{CH}_3$), and 0.75 (s, 3H, $-\text{CH}_3$); Cmr δ216.7, 134.4, 118.8, 53.5, 45.8, 43.3, 40.2, 36.1, 32.3, 31.1, 30.7, 23.5, 22.2, and 19.0; ir 1700 (C=O), 1391, 1378, 1368 (CH_3), and 784 cm^{-1} (C=CH); ms M^+ 206.1676 (calcd. for $C_{14}H_{22}O$: 206.1671).

2,9,9-Trimethyl-3,4,4aα,6,7,8,9,9aβ-octahydro-(5H)-benzocyclohepten-5-one (33), 2,9,9-trimethyl-1,4,4aβ,6,7,8,9,9aβ-octahydro-(5H)-benzocyclohepten-5-one (39) and 2,9,9-trimethyl-3,4,4aα,6,7,8,9,9aβ-octahydro-(5H)-benzocyclohepten-5-one (58)

Ketone 57[**] (831 mg, 4.03 mmol) was dissolved in dry benzene (25 ml) under an atmosphere of nitrogen. *p*-Toluene-sulfonic acid monohydrate (393 mg, 2.02 mmol) was added and the mixture heated at reflux with stirring. After 3 hr. the mixture was cooled to room

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[*] On one occasion using 4.0 equivalents of lithium iodide dihydrate-collidine reagent, and heating for 90 min. a yield of 97% was obtained based on consumption of 73% of the starting material.

[**] The conditions described produced an identical mixture of products in identical yield when applied to a mixture of ketones 57, 58 and 39.

temperature and diluted with ether. The resulting solution was washed with saturated aqueous sodium bicarbonate and water, dried, filtered and concentrated. Flash chromatography[36] of the residue on silica gel eluting with 6% ethyl acetate in petroleum ether gave pure ketone <u>33</u> (98 mg, 12% yield) as an oil: nmr δ5.48 (br s, 1H, C=CH), 2.56 (dd, 1H, J = 8, J' = 4 Hz, CO–CH–), 1.69 (s, 3H, C=C–CH_3), 1.05 (s, 3H, CH_3), and 0.91 (s, 3H, CH_3): Cmr δ218.0, 134.5, 122.3, 48.1, 45.3, 44.7, 38.1, 36.5, 31.2, 29.9, 27.2, 25.3, 23.9, and 21.8; ir 1693 (C=O), 1391, 1378, 1362 (CH_3), and 829 cm^{-1} (C=CH); ms M^+ 206.1675 (calcd. for $C_{14}H_{22}O$: 206.1671). <u>Anal.</u> Calcd. for $C_{14}H_{22}O$: C 81.50, H 10.75; Found: C 81.34, H 10.40. Continued elution gave a mixture of ketones <u>33</u>, <u>57</u>, <u>58</u> and <u>39</u> (35 mg, 4% yield). Continued elution gave a mixture of ketones <u>57</u>, <u>58</u> and <u>39</u> (700 mg, 84% yield). The total yield of ketones <u>33</u>, <u>57</u>, <u>58</u> and <u>39</u>, obtained was 100%.

<u>2,9,9-Trimethyl-1,4,4aβ,6,7,8,9,9aβ-octahydro-(5H)-benzocyclohepten-5-one (39)</u>

Ketone <u>57</u> (20 mg, 0.097 mmol) was dissolved in methanol (5 ml) under an atmosphere of nitrogen and 1.0 N aqueous sodium hydroxide solution (1.0 ml) was added. The solution was heated at reflux with stirring for 48 hr., then cooled to room temperature, diluted with water and extracted with ether. The extracts were washed with water, dried, filtered and concentrated to give a mixture of *cis*-

and *trans*-ketones 39 and 57 (16 mg, 80% yield). Continued elution gave pure *cis*-ketone 39 (2 mg, 10% yield) as an oil: nmr δ5.26 (m, 1H, =CH–), 2.82 (m, 1H, –CO–CH–), 1.70 (s, 3H, =C–CH$_3$), 1.12 (s, 3H, –CH$_3$), and 1.00 (s, 3H, –CH$_3$); ir 1696 (C=O), 1389, 1377, 1367 (CH$_3$), and 793 cm^{-1} (C=CH); ms M$^+$ 206.1667 (calcd. for $C_{14}H_{22}O$: 206.1670).

2,9,9-Trimethyl-3,4,4aα,6,7,8,9,9aβ-octahydro-(5H)-benzocyclohepten-5-one (58)

Ketone 33 (17 mg, 0.083 mmol) was dissolved in methanol (5 ml) under an atmosphere of nitrogen and 1.0 N aqueous sodium hydroxide (0.50 ml) was added. The mixture was heated at reflux with stirring for 20 hr. Then the reaction mixture was cooled to room temperature, diluted with water and extracted with ether. The extracts were washed with water, dried, filtered and concentrated to give a mixture of *cis*- and *trans*-ketones 33 and 58 (20:80 by nmr integration, 13 mg, 77% yield). The nmr of this product mixture showed two sets of signals; a minor set identical with those already reported for *cis*-ketone 33 and a major set attributed to the *trans*-ketone 58: nmr δ5.26 (br s, 1H, =CH–), 1.70 (s, 3H, =C–CH$_3$), 1.04 (s, 3H, –CH$_3$), and 0.80 (s, 3H, –CH$_3$); Cmr δ216.9, 135.7, 122.5, 47.8 (two carbons), 43.0 (two carbons), 37.0, 30.3, 29.8, 26.5, 24.6, 22.4, and 18.0. The following data were also recorded for the mixture of *cis*- and *trans*-ketones 33 and 58: ir 1704 (C=O), 1390, 1365 (CH$_3$), and

828 cm^{-1} (C CH); ms M^+ 206.1669 (calcd. for $C_{14}H_{22}O$: 206.1671).

7-Epihimachalol (60)

A 0.25 N solution of methyl lithium in ether (4.34 ml, 1.08 mmol) was added to ether (10 ml, distilled over lithium aluminum hydride). A solution of ketone 33 (149 mg, 0.72 mmol) in dry ether (10 ml) was added dropwise with stirring over 5 min. After stirring for an additional 30 min. the reaction mixture was poured into ice and water (∿20 ml) and the resulting mixture was extracted with ether. The extracts were washed with water, dried, filtered and concentrated. Column chromatography of the residue on silica gel, eluting with 5% ether in petroleum ether, gave alcohol 60 (149 mg, 93% yield) which crystallized on standing. One recrystallization from petroleum ether gave white crystals of pure alcohol 60: mp 60-68°C; nmr δ5.50 (br s, 1H, C=CH), 1.70 (s, 3H, $=\overset{|}{\mathrm{C}}-\mathrm{CH}_3$), 1.24 (s, 3H, $\mathrm{HO}-\underset{|}{\overset{|}{\mathrm{C}}}-\mathrm{CH}_3$), and 0.97 (s, 6H, 2x-$CH_3$); ir: 3461 (OH), 1387, 1376, 1363 (CH_3), and 856 cm^{-1} (C=CH); ms m/e (M^+-H_2O) 204.1880 (calcd. for $C_{15}H_{24}$: 204.1878). Anal. Calcd. for $C_{15}H_{26}O$: C 81.02, H 11.79; Found: C 81.14, H 11.55.

α-Himachalene (2) and β-Himachalene (3)

Alcohol 60 (103 mg, 0.464 mmol) was dissolved in dry pyridine (4 ml) under an atmosphere of nitrogen and the resulting solution was heated to reflux. A solution of phosphoryl chloride (142 mg, 0.928 mmol) in pyridine (1 ml) was added to the refluxing solution and the mixture was heated with stirring for 1 hr. The mixture was cooled to 0°, poured into cold 5% aqueous hydrochloric acid and extracted with ether. The extracts were washed with ice-cold aqueous 5% hydrochloric acid and water, dried, filtered and concentrated. Column chromatography of the residue on neutral alumina (Woelm I), eluting with petroleum ether, gave a mixture of himachalenes <u>2</u> and <u>3</u> (88 mg, 93% yield) in a ratio of 75:25 by nmr integration. A sample of a similar mixture (130 mg) was purified by flash chromatography[36] on silica gel eluting with petroleum ether. The fractions obtained in order of elution contained: a) pure α-himachalene (56 mg), b) α- and β-himachalene, 50:50, (40 mg), c) α- and β-himachalene, 40:60, (17 mg), and d) β-himachalene, 80% pure, (4 mg). α-Himachalene showed the following spectral data: nmr δ5.43 (br s, 1H, $=CH-$), 4.70 (m, 2H, $=CH_2$), 1.68 (d, 3H, J = 1.5 Hz, $=C-CH_3$), 1.01 (s, 3H, $-CH_3$), and 0.97 (s, 3H, $-CH_3$); ir (neat) 3060, 1775, 1626 ($C=CH_2$), 1390, 1379, 1362 (CH_3), 885 ($C=CH_2$), 868 ($C=CH$), and 822 cm^{-1} ($C=CH_2$); ms M^+ 204.1874 (calcd. for $C_{15}H_{24}$: 204.1878). The sample of β-himachalene (<u>3</u>) showed the following spectral data: nmr δ5.37 (br s, 1H, $=CH-$), 2.84 (br s, 1H, $=CH-\overset{|}{C}\underline{H}-\overset{|}{C}=$), 1.74 (s, 3H, $=C-CH_3$), 0.99 (s, 3H, $-CH_3$), and 0.75 (s, 3H, $-CH_3$); ms M^+ 204.1876 (calcd. for $C_{15}H_{24}$: 204.1878).

8aβ-Carbomethoxy-1,1-ethylenedioxo-4,4,6-trimethyl-1,2,3,4,4aβ,5,8,8a-octahydronaphthalene (61)

Ketone 44 (1.01 g, 4.02 mmol) was dissolved in dry benzene (50 ml) and ethylene glycol (2.78 g, 45 mmol) and *p*-toluenesulfonic acid monohydrate (10 mg, 0.053 mmol) were added. The reaction flask was fitted with a Dean-Stark water separator with type 3Å molecular seive in the take-off arm. The reaction mixture was heated at reflux for 47 hr. then cooled to room temperature. Saturated aqueous sodium bicarbonate (2 ml) was added and the resulting mixture was extracted with methylene chloride. The extracts were washed with water, dried, filtered and concentrated. Column chromatography of the residue on silica gel, eluting with 7-30% ether in petroleum ether, gave ketal 61 (1.09 g, 93% yield): nmr δ5.20 (dm, 1H, J = 5 Hz, $=CH-$), 3.73 (m, 4H, $-O-CH_2-CH_2-O-$), 3.54 (s, 3H, $-O-CH_3$), 2.81 (dd, 1H, J = 17, J' = 5 Hz, C-8 Ha), 1.56 (s, 3H, $=\overset{|}{C}-CH_3$), 0.96 (s, 3H, $-CH_3$), and 0.80 (s, 3H, $-CH_3$); Cmr δ174.1, 133.3, 188.7, 111.5, 64.7, 64.5, 53.6, 52.0, 41.2, 37.6, 33.2, 32.9, 29.3, 28.9, 28.6, 23.5, and 21.3; ir 1728 ($C=O$), 1386, 1368 (CH_3), and 794 cm^{-1} ($C=CH$); ms M^+ 294.1833 (calcd. for $C_{17}H_{26}O_4$: 294.1830). Anal. Calcd. for $C_{17}H_{26}O_4$: C 69.36, H 8.90; Found: C 69.13, H 9.01.

Deketalization of Ketal 61

Ketal 61 (28 mg, 0.095 mmol) was dissolved in acetone (2 ml) and *p*-toluenesulfonic acid hydrate (2.0 mg, 0.0095 mmol) was added. After stirring for 14 days the mixture was diluted with water and extracted with methylene chloride. The extracts were washed with water, dried, filtered and concentrated. Column chromatography of the residue on silica gel, eluting with 1% ether in petroleum ether, gave keto-ester 44 (14 mg, 59% yield, 100% based on consumption of 54% of starting ketal 61). Further elution with 1-5% ether in petroleum ether gave recovered ketal 61 (13 mg, 46% recovery).

1,1-Ethylenedioxo-8aβ-hydroxymethylene-4,4,6-trimethyl-1,2,3,4,4aβ,5,8,-8a-octahydronaphthalene (63)

Ketal 61 (954 mg, 3.24 mmol) was dissolved in anhydrous ether (50 ml) and lithium aluminum hydride (369 mg, 9.71 mmol) was added. After 4.5 hr. the mixture was cooled to 0° and water (5 ml) was added dropwise. The resulting mixture was extracted with methylene chloride and the extracts were washed with water, dried, filtered and concentrated. Column chromatography of the residue on silica gel, eluting with 10-15% ether in petroleum ether, gave recovered ketal 61 (75 mg, 9% recovery). Further elution with 15-50% ether in petroleum ether gave alcohol 63 (721 mg, 84% yield, 92% based on consumption of 91% of the starting material) which crystallized on standing. Three recrystallizations from petroleum ether gave white crystals of pure alcohol 63 the melting point of which did not change on further recrystallization: mp 79-112°C; nmr δ5.14 (br s, 1H, $=CH{-}$), 3.95 (s, 4H, $-O{-}CH_2{-}CH_2{-}O{-}$), 3.51 (dd, 1H, J = 11, J' = 2 Hz, $HO{-}\overset{|}{C}H{-}\underline{H}$), 3.10 (dd, 1H, J = J' = 11 Hz, $HO{-}\overset{|}{C}H{-}\underline{H}$), 2.42 (dd, 1H, J = 11, J' = 2 Hz, $-OH$), 1.62 (br s, 3H, $=\overset{|}{C}{-}CH_3$), 0.97 (s, 3H, $-CH_3$), and 0.83 (s, 3H, $-CH_3$); Cmr δ133.0, 118.2, 115.2, 64.9, 64.3, 63.8, 43.0, 39.1, 38.1, 33.5, 32.9, 29.1, 27.9, 26.7, 32.5, and 22.1; ir 3546 (-OH), 1390, 1380, 1366 (CH_3), and 790 cm^{-1} ($C{=}CH$); ms M^+ 266.1886 (calcd. for $C_{16}H_{26}O_3$: 266.1882). *Anal.* Calcd. for $C_{16}H_{26}O_3$: C 72.14, H 9.84; Found: C 71.85, H 9.85. After exchanging the nmr sample with D_2O, the following changes were observed in the nmr spectrum: δ3.51 (d, 1H, J = 11 Hz, $DO{-}\overset{|}{C}H{-}\underline{H}$), 3.10 (d, 1H, J = 11 Hz, $DO{-}\overset{|}{C}H{-}\underline{H}$), and the disappearance of the signal at δ2.42.

1,1-Ethylenedioxo-8aβ-(*N,N,N',N'*-tetramethylphosphorodiamidyloxymethylene)-4,4,6-trimethyl-1,2,3,4,4aβ,5,8,8a-octahydronaphthalene (66)

Alcohol 63 (515 mg, 1.94 mmol) was dissolved in a 20% solution of *N,N,N',N'*-tetramethylethylenediamine (distilled over sodium) in 1,2-dimethoxyethane (freshly distilled over lithium aluminum hydride) (19.4 ml of solution) under an atmosphere of nitrogen. The resulting solution was cooled to 0° and a 1.99 N solution of n-butyllithium in hexane (1.47 ml, 2.92 mmol) was added dropwise with stirring over 5 min. The mixture was allowed to warm to room temperature over 10 min. then *N,N*-dimethylphosphoramidic dichloride[38] was added. After 23 hr. the mixture was cooled to 0° and dimethylamine gas was passed through a potassium hydroxide drying tube and condensed

(60 drops, ~3 ml) into the reaction mixture. After 30 min. the resulting mixture was poured into ice-cold water and extracted with ether. The extracts were washed with water until the washings were neutral to pH paper, dried, filtered and concentrated. Column chromatography of the residue on silica gel, eluting with 5-20% methanol in ether, gave TMPDA derivative 66 (652 mg, 84% yield) which crystallized on standing. One recrystallization from ether gave colourless rhombic crystals of pure TMPDA derivative 66 (330 mg): mp 100-102°; nmr δ5.20 (br. s, 1H, =CH–), 4.18-3.73 (complex, total 5H, –O–C$\underline{H}_2$–C$\underline{H}_2$–O– and $\underline{\mathrm{H}}$–$\overset{|}{\mathrm{C}}$H–O–), 3.39 (dd, 1H, J ≈ 11, J' = 4 Hz, $\underline{\mathrm{H}}$–$\overset{|}{\mathrm{C}}$H–O–), 2.57, 2.55 (both d, total 12H, each J = 10 Hz, 2x –N(CH_3)$_2$), 1.64 (br. s, 3H, =$\overset{|}{\mathrm{C}}$–CH_3), 0.93 (s, 3H, –CH_3), and 0.81 (s, 3H, –CH_3); ir 1383, 1372, 1359 (CH_3), 1296 cm^{-1} (P=O); ms M^+ 400.2487 (calcd. for $C_{20}H_{37}N_2O_4P$: 400.2491). Anal. Calcd. for $C_{20}H_{37}N_2O_4P$: C 59.98, H 9.31, N 6.99; Found: C 59.89, H 9.48, N 6.77.

1,1-Ethylenedioxo-4,4,6,8aβ-tetramethyl-1,2,3,4,4aβ,5,8,8a-octahydronaphthalene (64)

Ethylamine (400 ml) was distilled from lithium into a reaction vessel under an atmosphere of argon. Small pieces of lithium ribbon (2.74 g, 392 mmol) were added and the mixture was stirred for 1 hr. to effect solution. Then a solution of TMPDA derivative 66 (15.7 g, 39.2 mmol) and *t*-butanol (5.80 g, 78.4 mmol, dried over type 3Å molecular seives) in tetrahydrofuran (270 ml, freshly distilled over lithium aluminum hydride) was added dropwise over 1 hr. with stirring. After an additional 40 min. water was added slowly to discharge the blue colour and the reaction mixture was poured into ice-cold water. The resulting mixture was extracted with ether and the extracts were washed with ice-cold water until the washings were neutral. The extracts were then dried, filtered and concentrated. Column chromatography of the residue on silica gel, eluting with 2% ether in petroleum ether, gave ketal 64 (6.75 g, 69% yield) which crystallyzed on standing. One recrystallization from petroleum ether gave colourless rhombs of pure ketal 64: mp: 28-30°C; nmr δ5.22 (br. s, 1H, $=CH-$), 3.86 (s, 4H, $-O-CH_2-CH_2-O-$), 1.62 (br. s, 3H, $=\overset{|}{C}-CH_3$), 0.88 (s, 3H, $-CH_3$), 0.83 (s, 3H, $-CH_3$), and 0.76 (s, 3H, $-CH_3$); ir 1388, 1371, 1363 (CH_3) and 780 cm^{-1} ($C=CH$); ms M^+ 250.1930 (calcd. for $C_{16}H_{26}O_2$: 250.1933). Anal. Calcd. for $C_{16}H_{26}O_2$: C 76.75, H 10.47; Found: C 76.82, H 10.56. Further elution with 2-5% ether in petroleum ether gave *trans*-ketone 49 (354 mg, 5% yield) and further elution with 5-100% ether in petroleum ether gave alcohol 63 (1.42 g, 14% yield).

4,4,6,8aβ-Tetramethyl-3,4,4aβ,5,8,8a-hexahydro-1(2H)-naphthalenone (45)

Ketal 64 (265 mg, 1.06 mmol) was dissolved in acetone (20 ml) and *p*-toluenesulfonic acid monohydrate (110 mg, 0.53 mmol) was added. The resulting mixture was stirred for 150 min. and then diluted with methylene chloride. The resulting solution was washed with saturated aqueous sodium bicarbonate and water, dried, filtered and concentrated. Column chromatography on silica gel, eluting with 2-8% ether in petroleum ether, gave pure ketone <u>45</u> (211 mg, 97% yield): nmr δ5.27 (m, 1H, =CH–), 2.68 (ddd, 1H, J = 15, J' = 12, J" = 8 Hz, –CO–CH–<u>H</u>b), 2.08 (ddd, 1H, J = 15, J' = J" = 4 Hz, CO–CH–Ha), 1.65 (s, 3H, =C–CH_3), 1.02 (s, 3H, –CH_3), and 0.95 (s, 6H, 2x –CH_3); Cmr δ216.2, 132.1, 117.7, 48.9, 46.4, 40.7, 34.9, 33.7, 32.2, 28.0, 23.6, 23.2, and 21.0; ir 1706 (C=O), 1390, 1375 (CH_3), 820 and 790 cm^{-1} (C=CH); ms M^+ 206.1671 (calcd. for $C_{14}H_{22}O$: 206.1671). <u>Anal.</u> Calcd. for $C_{14}H_{22}O$: C 81.50, H 10.75; Found: C 81.77, H 10.74.

<u>4,4,6,8aβ-Tetramethyl-3,4,4aβ,7,8,8a-hexahydro-1(2*H*)-naphthalenone (67)</u>

Ketone <u>45</u> (758 mg, 3.68 mmol) was dissolved in benzene (50 ml) under an atmosphere of nitrogen and *p*-toluenesulfonic acid hydrate (350 mg, 1.84 mmol) was added. The mixture was heated to reflux with stirring for 2 hr. and then cooled to room temperature, diluted with water and extracted with methylene chloride. The extracts were washed with saturated aqueous sodium bicarbonate and water, dried, filtered and concentrated. Column chromatography of the residue on silica gel, eluting with 2-4% ether in petroleum ether, gave a mixture of ketones <u>67</u> and <u>45</u> (85:15 by gc analysis, 67.5 mg, 89% yield). The nmr and and Cmr spectra of this mixture showed the following signals which were attributed to ketone <u>67</u>: nmr δ5.40 (m, 1H, =CH–), 1.71 (s, 3H,

$=\overset{|}{C}-CH_3$), 1.04 (s, 3H, $-CH_3$), 0.97 (s, 3H, $-CH_3$), and 0.94 (s, 3H, $-CH_3$); Cmr δ217.3, 133.7, 120.5, 52.3, 46.0, 38.5, 35.1, 34.0, 29.3, 26.2, 23.8, 23.1, and 22.8. The following spectra were also recorded: ir 1703 (C=O), 1384, 1374, 1362 cm^{-1} (CH_3); ms M^+ 206.1672 (calcd. for $C_{14}H_{22}O$: 206.1670). Anal. Calcd. for $C_{14}H_{22}O$: C 81.50, H 10.75; Found: C 81.48, H 10.95.

6-Carboethoxy-2,4aβ,9,9-tetramethyl-3,4,4a,6,7,8,9,9aβ-octahydro-(5*H*)-benzocyclohepten-5-one (69)

Ketone 67* (42 mg, 0.20 mmol) was dissolved in ether (4 ml) in a flask wrapped in aluminum foil to exclude light. Boron trifluoride etherate (145 mg, 1.02 mmol) was added followed by ethyl diazoacetate (107 μl, 116 mg, 1.02 mmol). After stirring for 4 days additional boron trifluoride etherate (145 mg, 1.02 mmol) and ethyl diazoacetate (116 mg, 1.02 mmol) were added. After a further 3 days saturated aqueous sodium bicarbonate (1 ml) was added and the resulting mixture was extracted with methylene chloride. The extracts were washed with water, dried, filtered and concentrated. Column chromatography of the residue on silica gel, eluting with 2% ether in petroleum ether, gave ketone 67 (3 mg, 7% recovery). Continued elution gave keto-ester 69 (12 mg, 20% yield, 21% based on recovered ketone 67):

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*This material was contaminated with ∿15% of the isomeric ketone 45.

nmr δ5.32 (d, 1H, J = 5 Hz, $=CH-$), 4.09, 4.07 (both q, total 2H, both J = 7 Hz, $-O-C\underline{H}_2-CH_3$), 3.92 (dd, 1H, J = 12, J' = 4 Hz, $-CO-\overset{|}{C}H-CO_2-$), 1.71 (br. s, 3H, $=\underset{|}{C}-CH_3$), 1.21 (dd, 3H, J = J' = 7 Hz, $-O-CH_2-C\underline{H}_3$), 1.09 (s, 3H, $-CH_3$), 0.97 (s, 3H, $-CH_3$), and 0.67 (s, 3H, $-CH_3$); ir 1748 (ester C=O), 1706 (ketone C=O), 1389 and 1367 (CH_3); ms M^+ 292.2031 (calcd. for $C_{18}H_{28}O_3$: 292.2039). Continued elution gave keto-ester 70 (11 mg, 19% yield, 20% based on recovered ketone 67).

2,4aβ,9,9-Tetramethyl-3,4,4a,6,7,8,9,9aβ-octahydro-(5H)-benzocyclohepten-5-one (15) via Keto-ester 69

Keto-ester 69 (23 mg, 0.078 mmol) was dissolved in lithium iodide dihydrate–collidine reagent (244 μl, 0.312 mmol) and heated to reflux. After 45 min. the mixture was cooled to room temperature, poured into cold aqueous 5% hydrochloric acid and extracted with ether. The extracts were washed with 5% hydrochloric acid and water, dried, filtered and concentrated. Column chromatography of the residue on silica gel, eluting with 1% ether in petroleum ether, gave ketone 15 (1.4 mg, 10% yield based on recovered 69). Further elution with 2-5% ether in petroleum ether gave keto-ester 69 (5.4 mg, 23% recovery).

6-Carboethoxy-2,4aβ,9,9-tetramethyl-1,4,4a,6,7,8,9,9aβ-octahydro-(5H)-benzocyclohepten-5-one (70)

Ketone 45 (178 mg, 0.86 mmol) was dissolved in anhydrous ether (5 ml) in a flask wrapped in aluminum foil to exclude light. Boron trifluoride etherate (491 mg, 3.46 mmol) was added followed by ethyl diazoacetate (394 mg, 3.46 mmol). After stirring for 48 hr. the reaction mixture was cooled to 0° and saturated aqueous sodium bicarbonate (2 ml) was added. The resulting mixture was extracted with methylene chloride and the extracts were washed with water, dried, filtered and concentrated. Column chromatography of the residue on silica gel eluting with 3-5% ether in petroleum ether gave keto-ester 70* (205 mg, 82% yield) which crystallized on standing. One recrystallization from ether gave white crystals of pure keto-ester 70: mp 76-78°C; nmr δ5.34 (br. s, 1H, $=CH-$), 4.11, 4.08 (both q, total 2H, both J = 7 Hz, $-O-CH_2-$), 3.86 (dd, 1H, J = J' = 10 Hz, $-CO-\overset{|}{C}\underline{H}-CO_2-$), 2.10 (br. s, 4H, 2x $=\overset{|}{C}-CH_2-$), 1.66 (s, 3H, $=\overset{|}{C}-CH_3$), 1.22 (dd, 3H, J = J' = 7 Hz, $-O-CH_2-C\underline{H_3}$), 1.09 (s, 3H, $-CH_3$), 0.98 (s, 3H, $-CH_3$), and 0.71 (s, 3H, $-CH_3$); nmr (200 MHz, $CDCl_3$) δ: 5.35 (br. s, 1H, $=CH-$), 4.20, 4.19 (both q, total 2H, both J = 7 Hz, $-O-CH_2-$), 4.14 (dd, 1H, J = J' = 10 Hz, $-CO-\overset{|}{C}\underline{H}-CO_2-$), 2.20 (br. s, 4H, 2x $=\overset{|}{C}-CH_2-$), 1.68 (s, 3H, $=\overset{|}{C}-CH_3$), 1.24 (dd, 3H, J = 7 Hz, $-O-CH_2-C\underline{H_3}$), 1.15 (s, 3H, $-CH_3$), 0.99 (s, 3H, $-CH_3$), and 0.72 (s, 3H, $-CH_3$); Cmr δ212.1, 170.8, 132.0, 119.2, 61.0, 50.3, 49.5, 44.7, 37.3, 37.1, 29.6, 29.3

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*This material required 24 hr. under vacuum (0.5 Torr) to remove an inpurity which is thought to be ethyl glycolate on the basis of the nmr spectrum of the mixture.

(two carbons), 26.0, 25.9, 23.1, 20.8, and 14.1; ir 1750 (ester C=O), 1700 (ketone C=O), 1392, 1364 (CH_3), 791 cm^{-1} (C=CH); ms M^+ 292.2037 (calcd. for $C_{18}H_{28}O_3$: 292.2038). Anal. Calcd. for $C_{18}H_{28}O_3$: C 73.93, H 9.65; Found: C 73.75, H 9.61.

2,4aβ,9,9-Tetramethyl-1,4,4a,6,7,8,9,9aβ-octahydro-(5H)-benzocyclohepten-5-one (68)

Keto-ester 70 (166 mg, 0.57 mmol) was dissolved in 2,4,6-collidine (1.8 ml) under an atmosphere of nitrogen. Lithium iodide (304 mg, 2.27 mmol) and water (82 µl, 4.54 mmol) were added and the mixture was heated to reflux with stirring for 2 hr. The reaction mixture was then cooled to room temperature, poured into cold aqueous 5% hydrochloric acid and extracted with ether. The extracts were washed with aqueous 5% hydrochloric acid and water, dried, filtered and concentrated. Column chromatography of the residue on silica gel, eluting with 2-3% ether in petroleum ether, gave ketone 73 (108 mg, 86% yield) which crystallized on standing. One recrystallization from petroleum ether gave white clusters of pure ketone 68 (63 mg): mp 53-56°C; nmr δ5.30 (br. s, 1H, $=CH-$), 2.84 (ddd, 1H, J = 11, J' = J" = 9 Hz, $-CO-\overset{|}{C}H-\underline{H}$), 1.63 (br. s, 3H, $=\overset{|}{C}-CH_3$), 0.97 (s, 3H, $-CH_3$), 0.95 (s, 3H, $-CH_3$), and 0.69 (s, 3H, $-CH_3$); Cmr δ217.8, 132.1, 119.7, 49.1, 45.0, 38.2, 37.5, 35.4, 30.1, 29.6, 29.5, 26.6, 26.1, 23.1, and 18.1; ir (1701 (C=O), 1387, 1372, 1362 (CH_3), and 838 cm^{-1} (C=CH); ms M^+ 220.1829 (calcd. for $C_{15}H_{20}O$: 220.1827). Anal. Calcd. for $C_{15}H_{20}O$:

C 81.76, H 10.98; Found: C 81.63, H 10.87.

2,4aβ,9,9-Tetramethyl-3,4,4a,6,7,8,9,9aβ-octahydro-(5H)-benzocyclohepten-5-one (15) via Ketone 68

Ketone 68 (20 mg, 0.09 mmol) was dissolved in dry benzene (5 ml) under an atmosphere of nitrogen. *p*-Toluenesulfonic acid hydrate was added and the mixture was heated to reflux for 2 hr. The reaction mixture was then cooled to room temperature, poured into water and extracted with ether. The extracts were washed with water, dried, filtered and concentrated. Column chromatography of the residue on silica gel, eluting with 0.5% ether in petroleum ether gave a ketone (Ketone A, 3 mg, 15% yield), the structure of which was not determined but which showed the following spectroscopic data: nmr δ5.17 (m, 1H, =CH–), 1.60 (s, 3H, $=\overset{|}{C}-CH_3$), 1.26 (s, 3H, $-CH_3$), 0.94 (s, 3H, $-CH_3$), and 0.75 (s, 3H, $-CH_3$); ir 1699 (C=O), 1384, 1377 and 1364 (CH_3); ms M^+ 220.1831 (calcd. for $C_{15}H_{24}O$: 220.1827). Continued elution gave ketone 15 (10.6 mg, 53% yield) which crystallized on standing: mp 48-54°C; nmr δ5.34 (d, 1H, J = 4 Hz, =CH–), 2.66 (ddd, 1H, J = J' = 10, J" = 4 Hz, $=\overset{|}{C}H-H$), 1.69 (br. s, 3H, $=\overset{|}{C}-CH_3$), 1.01 (s, 3H, $-CH_3$), 0.97 (s, 3H, $-CH_3$), and 0.69 (s, 3H, $-CH_3$); Cmr δ218.0, 134.1, 121.8, 50.2, 49.7, 46.2, 40.5, 39.6, 33.4, 27.1, 25.7, 24.5, 23.4 (two carbons)*; ir (1699 (C=O), 1388, 1365 (CH_3), and

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*The fifteenth signal, which was expected to appear at ∿δ27 to δ28 was probably obscured by the signal at δ27.7 due to cyclohexane which was used as an internal reference in this case.

870 cm^{-1} (C=CH); ms M^{+} 220.1823 (calcd. for $C_{15}H_{24}O$: 220.1827). Further elution with 1% ether in petroleum ether gave recovered ketone 68 (1 mg, 5% recovery).

1,1-Ethylenedioxo-6-formyl-4,4,8aβ-trimethyl-1,2,3,4,4aβ,5,8,8a-octahydronaphthalene (75), 1,1-Ethylenedioxo-6-formyl-4,4,8aβ-trimethyl-1,2,3,4,4aβ,8a-hexahydronaphthalene (76), 1,1-Ethylenedioxo-6-hydroxymethylene-4,4,8aβ-trimethyl-1,2,3,4,4aβ,5,8,8a-octahydronaphthalene (77) and 1,1-Ethylenedioxo-8-hydroxy-4,4,6,8aβ-tetramethyl-1,2,3,4,4aβ,5,8,8a-octahydronaphthalene (78)

Ketal 64 (106 mg, 0.42 mmol) was dissolved in *t*-butanol (10 ml) and selenium dioxide (47 mg, 0.424 mmol) was added. The mixture was heated at reflux for 24 hr. then cooled to room temperature, filtered and concentrated. Column chromatography of the residue on silica gel, eluting with 2% ether in petroleum ether, gave recovered ketal 64 (34 mg, 32% recovery). Further elution with 5% ether in petroleum ether gave aldehyde 76 (13 mg, 18% yield based on recovered 64): nmr δ9.42 (s, 1H, —CHO), 6.54 (d, 1H, J = 7 Hz, $-C\underline{H}=\overset{|}{C}-CO-$), 6.30 (dd, 1H, J = 10 J' = 1 Hz, $-\underline{H}C=CH-$), 6.12 (d, 1H, J = 10 Hz, $-HC=C\underline{H}-$), 3.92 (complex, total 4H, $-O-CH_2-CH_2-O-$), 2.30 (d, 1H, J = 7 Hz, $-\overset{|}{C}\underline{H}-CH=$), 1.00 (s, 3H, $-CH_3$), 0.93 (s, 3H, $-CH_3$), and 0.80 (s, 3H, $-CH_3$); ir 2805, 2712 (aldehydic C—H), 1688 (C=O), 1389 and 1363 (CH_3); ms M^{+} 262.1559 (calcd. for $C_{16}H_{22}O_3$: 262.1569). Further elution with

5-10% ether in petroleum ether gave aldehyde 75 (26 mg, 34% based on recovered 64): nmr δ9.37 (s, 1H, $-CHO$), 6.61 (m, 1H, $-C\underline{H}=$), 3.92 (s, 4H, $-O-CH_2-CH_2-O-$), 0.96 (s, 3H, $-CH_3$), 0.86 (s, 3H, $-CH_3$), and 0.70 (s, 3H, $-CH_3$); ir 2810, 2720 (aldehydic C–H), 1676 (C=O), 1647 (C=C), 1393, 1382 and 1371 (CH_3); ms M^+ 264.1728 (calcd. for $C_{16}H_{24}O_3$: 264.1725). Anal. Calcd. for $C_{16}H_{24}O_3$: C 72.69, H 9.15; Found C 72.57, H 9.12. Further elution with 20% ether in petroleum ether gave alcohol 78 (12 mg, 16% based on recovered ketal 64): δ5.12 (d, 1H, J = 2 Hz, $=CH-$), 4.44 (br. s, 1H, $-\overset{|}{C}\underline{H}-OH$), 3.91 (complex, 4H, $-O-CH_2-CH_2-O-$), 2.90 (s, 1H, $-OH$), 1.65 (s, 3H, $=\overset{|}{C}-CH_3$), 0.88 (s, 3H, $-CH_3$), 0.82 (s, 3H, $-CH_3$), and 0.73 (s, 3H, $-CH_3$); ir 3531 (OH), 1391 and 1376 (CH_3); ms M^+ 266.1887 (calcd. for $C_{16}H_{26}O_3$: 266.1881). Further elution with 50% ether in petroleum ether gave alcohol 77 (25 mg, 32% based on recovered ketal 64): nmr δ5.50 (br. s, 1H, $=CH-$), 3.90 (s, 7H total, $-O-C\underline{H}_2-C\underline{H}_2-O-$ and $-C\underline{H}_2-O\underline{H}$), 0.94 (s, 3H, $-CH_3$), 0.86 (s, 3H, $-CH_3$), and 0.80 (s, 3H, $-CH_3$); ir 3422 (OH), 1391 and 1367 (CH_3); ms M^+ 266.1884 (calcd. for $C_{16}H_{26}O_3$: 266.1881).

1,1-Ethylenedioxo-4,4,6,8aβ-tetramethyl-1,2,3,4,4aβ,7,8,8a-octahydronaphthalene (79)

From Ketone 67

Ketone 67* (629 mg, 305 mmol) was dissolved in dry benzene (50 ml)

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*This material was contaminated with ~15% of the double bond isomer.

under an atmosphere of argon. Ethylene glycol (1.89 g, 3.05 mmol) was added followed by *p*-toluenesulfonic acid hydrate (58 mg, 0.305 mmol). The mixture was heated at reflux with vigorous stirring and with removal of water via a Dean-Stark trap charged with type 3Å molecular seive. After heating for 18 hr. the reaction mixture was cooled to ∿5°C and poured into saturated aqueous sodium bicarbonate. The resulting mixture was extracted with methylene chloride and the extracts were washed with water, dried, filtered and concentrated. Column chromatography of the residue on silica gel, eluting with 2-3% ether in petroleum ether, gave ketal 79* (730 mg, 96% yield, 99% based on consumption of 97% of the starting ketone 67) which crystallized in the refrigerator. One recrystallization from petroleum ether gave pure ketal 79: mp 30-32°C; nmr 5.37 (br. d, 1H, J = 5 Hz, $=CH-$), 4.86 (complex, 4H, $-O-CH_2-CH_2-O$), 1.70 (s, 3H, $=\overset{|}{C}-CH_3$), 0.97 (s, 3H, $-CH_3$), 0.84 (s, 3H, CH_3), and 0.79 (s, 3H, CH_3); ir 1386, 1374, 1362 (CH_3), and 812 cm^{-1} (CH_3); ms M^+ 250.1929 (calcd. for $C_{16}H_{22}O_2$: 250.1933). Anal. Calcd. for $C_{16}H_{26}O_2$: C 76.75, H 10.47; Found: C 76.97, H 10.54. Further elution with 3-5% ether in petroleum ether gave ketone 67 (18 mg, 3% recovery).

From Ketone 45

Ketone 45 (2.46 g, 11.96 mmol) was dissolved in benzene (150 ml)

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*This material was contaminated with ∿15% of the double bond isomer.

under an atmosphere of argon and *p*-toluenesulfonic acid hydrate (1.206 g, 5.35 mmol) was added. The mixture was heated at reflux for 2 hr. and then cooled. Ethylene glycol (7.87 g, 127 mmol) was added. This mixture was heated at reflux with water separation using a Dean-Stark trap. After heating for 21 hr. benzene (∿100 ml) was removed by distillation through the water separator. The residue was cooled to ∿5° and poured into saturated aqueous sodium bicarbonate (50 ml). The resulting mixture was extracted with methylene chloride and the extracts were washed with water, dried, filtered and concentrated. Column chromatography of the residue on silica gel, eluting with 2-3% ether in petroleum ether, gave ketal 79[*] (2.89 g, 96% yield, 98% based on recovery of 2% of the intermediate ketone 67) which could be further purified by recrystallization from petroleum ether. Further elution with 3-5% ether in petroleum ether gave intermediate ketone 67[*] (63 mg, 2% recovery).

1,1-Ethylenedioxo-6-formyl-4,4,8aβ-trimethyl-1,2,3,4,4aβ,7,8,8a-octahydronaphthalene (80), 1,1-Ethylenedioxo-6-formyl-4,4,8a-trimethyl-1,2,3,4,8,8a-hexahydronaphthalene (81) and 1,1-Ethylenedioxo-6-hydroxymethylene-4,4,8aβ-trimethyl-1,2,3,4,4aβ,7,8,8a-octahydronaphthalene (82)

Ketal 79 (686 mg, 2.74 mmol) was dissolved in *t*-butanol (50 ml) and selenium dioxide (609 mg, 5.49 mmol) was added. The mixture was

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[*] This material was contaminated with ∿15% of the double bond isomer.

heated at reflux for 40 hr. and then cooled to room temperature, filtered and concentrated. Column chromatography of the residue on silica gel, eluting with 2% ether in petroleum ether, gave ketal <u>79</u> (69 mg, 10% recovery). Further elution with 6-12% ether in petroleum ether gave aldehyde <u>80</u> (118 mg, 18% yield based on recovered ketal <u>79</u>): nmr δ9.42 (s, 1H, $-CHO$), 6.68 (ddd, 1H, J = 5, J' = J" - 2 Hz, $=CH-$), 3.90 (m, 4H, $-O-CH_2-CH_2-O-$), 1.10 (s, 3H, $-CH_3$), 0.85 (s, 3H, $-CH_3$), and 0.78 (s, 3H, $-CH_3$); ir 2805, 2710 (aldehydic C—H), 1686 (C═O), 1389 and 1369 cm^{-1} (CH_3); ms M$^+$ 264.1724 (calcd. for $C_{16}H_{24}O_3$: 264.1725). Further elution with 12% ether in petroleum ether gave aldehyde <u>81</u> (18 mg, 18% yield based on recovered ketal <u>79</u>) which crystallized on standing. One recrystallization from ether gave pure aldehyde <u>81</u>: mp 101.5-102.5°C; nmr δ9.32 (s, 1H, $-CHO$), 6.54 (ddd, 1H, J = 7, J' = 3, J" = 1 Hz, $-C\underline{H}=\overset{|}{C}-CHO$), 6.27 (s, 1H, $-C=C\underline{H}-\overset{\|}{C}-CHO$), 3.90 (m, 4H, $-O-C\underline{H}_2-C\underline{H}_2-O-$), 2.89 (dd, 1H, J = 18, J' = 3 Hz, $=CH-\overset{|}{C}H-\underline{H}$), 2.11 (dd, 1H, J = 18, J' = 7 Hz, $=CH-\overset{|}{C}H-\underline{H}$), 1.23 (s, 6H, 2x $-CH_3$), and 1.15 (s, 3H, $-CH_3$); ir 2807, 2712 (aldehydic C—H), 1682 (C═O), and 1365 cm^{-1} (CH_3); ms M$^+$ 262.1571 (calcd. for $C_{16}H_{22}O_3$: 262.1569). <u>Anal.</u> Calcd. for $C_{16}H_{22}O_3$: C 73.25, H 8.45; Found: C 72.97, H 8.34. Further elution with 20-50% ether in petroleum ether gave alcohol <u>82</u> (77 mg, 12% yield based on recovered ketal <u>79</u>): nmr δ5.65 (d, 1H, $=CH-$), 3.80 (complex, 7H total, $-O-CH_2-CH_2-O-$ and $-CH_2-OH$), 0.98 (s, 3H, $-CH_3$), 0.84 (s, 3H, $-CH_3$), and 0.79 (s, 3H, $-CH_3$): ir 3438 (OH), 1385, 1364 (CH_3), and 810 cm^{-1} (C═CH); ms M$^+$ 266.1890 (calcd. for $C_{16}H_{26}O_3$: 266.1882).

1,1-Ethylenedioxo-6-formyl-4,4,8aβ-trimethyl-1,2,3,4,4aβ,7,8,8a-octahydronaphthalene (80) from Alcohol 82

Pyridinium chlorochromate (244 mg, 1.13 mmol) and sodium acetate (52 mg, 0.38 mmol) were suspended in methylene chloride (10 ml) and a solution of alcohol 82 (200 mg, 0.75 mmol) and methylene chloride (10 ml) was added. After stirring for 1 hr. the mixture was poured into anhydrous ether (100 ml). The residue in the reaction flask was washed with ether and the combined ethereal mixtures were filtered. The resulting solution was passed through a column of florisil (∿3 gm) and concentrated. Column chromatography of the residue on silica gel, eluting with 5-6% ether in petroleum ether, gave aldehyde 80 (105 mg, 52% yield).

1,1-Ethylenedioxo-6-formyl-4,4,8aβ-trimethyl-1,2,3,4,4aα,7,8,8a-octahydronaphthalene (83)

cis-Aldehyde 80 (153 mg, 0.58 mmol) was dissolved in methanol (10 ml) under an atmosphere of argon. Then 1.0 N aqueous sodium hydroxide (2 ml) was added and the mixture heated to reflux. After 22 hr. the mixture was cooled to room temperature, poured into water and extracted with ether. The extracts were washed with water, dried, filtered and concentrated. Gc analysis of the residue showed *cis*- and *trans*-aldehydes 80 and 83 in a ratio of 52:48. Flash chromatography[36] of the residue, eluting with 13% ethyl acetate in petroleum ether gave *cis*-aldehyde 80 (46 mg). Continued elution gave an ∿40:60 mixture (26 mg) of 80 and 83. Continued elution gave pure *trans*-aldehyde 83: nmr δ9.37 (s, 1H, —CHO), 6.56 (ddd, 1H, J = J' = J" = 2 Hz), 3.85 (br. s, 4H, —O—CH_2—CH_2—O—), 1.01 (s, 3H, —CH_3), 0.90 (s, 3H, —CH_3), and 0.88 (s, 3H, —CH_3): ir 1683 (C=O) and 1379 (CH_3); ms M^+ 264.1725 (calcd. for $C_{16}H_{24}O_3$: 264.1725). The total yield of aldehydes 80 and 83 obtained was 69%.

References

1. G.S.K. Rao, S. Dev, and P.C. Guha, J. Indian. Chem. Soc., 29, 721 (1952).
2. T.C. Joseph and S. Dev, Tetrahedron Letters, 216 (1961).
3. J.B. Bredenberg and H. Erdtman, Acta Chem. Scand., 15, 685 (1961).
4. T.C. Joseph and S. Dev, Tetrahedron, 24, 3809 (1968).
5. T.C. Joseph and S. Dev, Tetrahedron, 24, 3841 (1968).
6. M. Plattier and P. Teisseire, Recherches, 19, 131 (1974).
7. M. Plattier, P. Rouillier, and P. Teisseire, Recherches, 19, 145 (1974).
8. M. Plattier and P. Teisseire, An. Acad. Bras. Cienc., 44, 392 (1972).
9. S.C. Bisarya and S. Dev, Tetrahedron, 24, 3861 (1968).
10. D.R. Adams, S.P. Bhatnagar, and R.C. Cookson, J. Chem. Soc., Perkin I, 1502 (1975).
11. R. Shankaranarayan, S.C. Bisarya, and S. Dev, Tetrahedron, 33, 1207 (1977).
12. D.K. Kulshreshtha and R.P. Rastogi, Phytochemistry, 14, 2237 (1975).
13. D.K. Kulshreshtha and R.P. Rastogi, Phytochemistry, 15, 557 (1976).
14. P. Teisseire and M. Plattier, Recherches, 19, 167 (1974).
15. R. Shankaranarayan, S. Krishnappa, and S. Dev, Tetrahedron, 33, 885 (1977).
16. S.C. Bisarya and S. Dev, Tetrahedron Letters, 3761 (1964).
17. S.C. Bisarya and S. Dev, Tetrahedron, 24, 3869 (1968).

18. W. Parker, J.S. Roberts, and R. Ramage, Quart. Rev., 21, 331 (1967).

19. Y. Pocker in P. de Mayo, "Molecular Rearrangements", Wiley, New York, 1963, page 1.

20. A.P.S. Narula and S. Dev, Tetrahedron, 33, 813 (1977).

21. R.C. Pandey and S. Dev, Tetrahedron, 24, 3829 (1968).

22. B.D. Challand, G. Kornis, G.L. Lange, and P. de Mayo, J. Chem. Soc. Chem. Comm., 704 (1967).

23. B.D. Challand, H. Hikino, G. Kornis, G. Lange, and P. de Mayo, J. Org. Chem., 34, 794 (1969).

24. E. Wenkert and K. Naemura, Syn. Comm., 3, 45 (1973).

25. E. Wenkert and Y. Gaioni, J. Org. Chem. 31, 3809 (1966).

26. E. Piers and E.H. Ruediger, J. Chem. Soc., Chem. Comm., 166 (1979).

27. H.J. Liu and E.N.C. Browne, Can. J. Chem., 57, 377 (1979).

28. J.A. Osborn, F.H. Jardine, J.F. Young, and G. Wilkinson, J. Chem. Soc, A, 1711 (1966).

29. I. Ojima, M. Nihonyanagi, T. Kogure, M, Kumagai, S. Horiuchi, K. Nakatsugawa, and Y. Nagai, J. Organometallic Chem., 94, 449 (1975).

30. I. Ojima, T. Kogure, M. Nihonyanagi, and Y. Nagai, Bull. Chem. Soc. Japan, 45, 3506 (1972).

31. F. Elzinger, Org. Syn., 45, 7 (1965).

32. W.T. Tai and E.W. Warnhoff, Can. J. Chem., 42, 1333 (1964).

33. H.J. Liu and T. Ogino, Tetrahedron Letters, 4937 (1973).

34. H.J. Liu and S.P. Majumdar, Syn. Comm., 5, 125 (1975).
35. T.C. Joseph and S. Dev., Tetrahedron, 24, 3853 (1968).
36. W.C. Still, M. Kahn and A. Mitra; J. Org. Chem., 43, 2923 (1978).
37. R.E. Ireland, D.C. Muchmore, and U. Hengartner, J. Amer. Chem. Soc., 94, 5098 (1972).
38. H.J. Liu, S.P. Lee, and W.H. Chan, Can. J. Chem., 55, 3797 (1977).
39. E.N. Walsh and A.D.F. Toy, Inorg. Syn., 7, 69 (1963).
40. J.B. Stothers, "Carbon-13 NMR Spectroscopy", Academic Press, New York, 1972.
41. S. Dev, personal communication.
42. P. Teisseire, personal communication.
43. E.N. Trachtenberg and J.R. Carver, J. Org. Chem., 35, 1970.
44. E.J. Corey and J.W. Suggs, Tetrahedron Letters, 2647 (1975).
45. R.M. Silverstein and G.C. Bassler, "Spectrometric Identification of Organic Compounds", 2nd ed., Wiley, New York, 1967.
46. G. Zweifel and H.C. Brown, Organic Reactions, 13, 28 (1963).
47. L.F. Fieser and M. Fieser, "Reagents for Organic Synthesis", Vol. 1, Wiley, New York, 1967.
48. H.J. Liu and E.N.C. Browne, Tetrahedron Letters, 2919 (1979).
49. H.E. Zimmerman, P. Hackett, D.F. Jones, J. McCall and B. Schröder, J. Amer. Chem. Soc., 93, 3653 (1971).

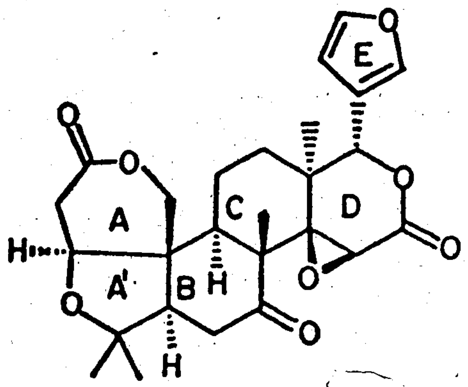
CHAPTER 3

Synthetic Studies on the AA'BC Ring System of Limonin

Introduction

Limonin, the characteristic bitter principle of citrus species, was first isolated by Bernays[1] from citrus seeds in 1841 and has since been found to occur in all parts of the plant[2]. Although investigation of its structure was not intensive prior to 1950[3] it remained one of the last "classical" problems of plant structural chemistry[2]. The early literature on these investigations was summarized by Arigoni[4] as well as by several other groups[2,3].

The elucidation of the structure of limonin was announced jointly by four research groups in 1960[3,5] and was based on classical structural studies[2,3] in conjunction with X-ray studies on a crystalline derivative[5,6]. On the basis of this work the structure and absolute stereochemistry were assigned as shown in 1.



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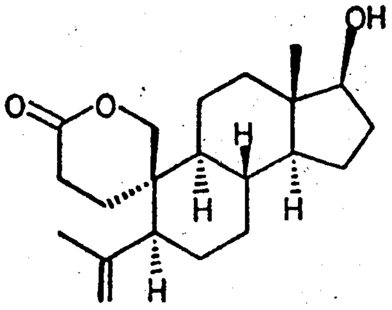
In a previous approach the AA' ring system of limonin (1) was generated from a steroid precursor[7,8]. The spirolactone 2 obtained in eleven steps from 19-hydroxytestosterone acetate (3), when treated with hydrofluoric acid at 4°C for 2 days gave cyclization product 4 in 92% yield. In a somewhat more laborious approach by



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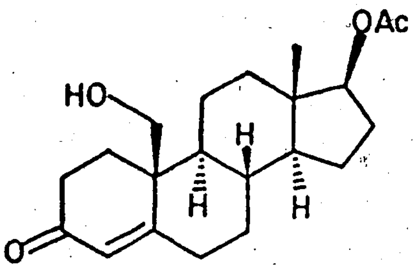

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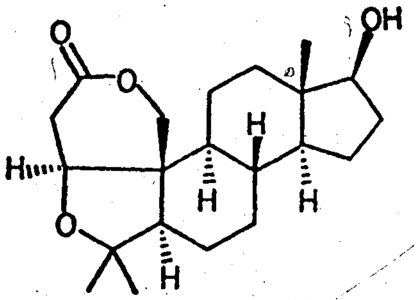

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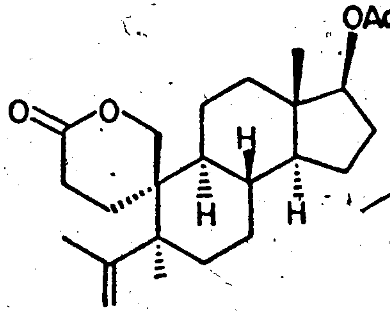
the same authors[7,8], the acetate derivative 5 obtained from spirolactone 2 was oxidized with osmium tetroxide. The resulting diol was found to cyclize under the reaction conditions to give alcohol 6. Tosylation of 6 followed by conversion of the tosylate to an iodide and reduction with Raney nickel gave the A,A' ring model 7.



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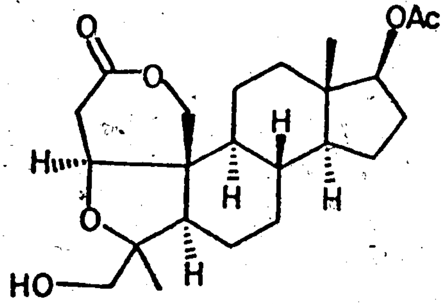

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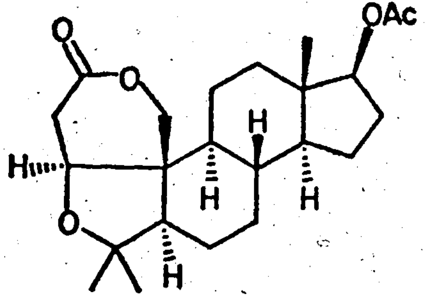

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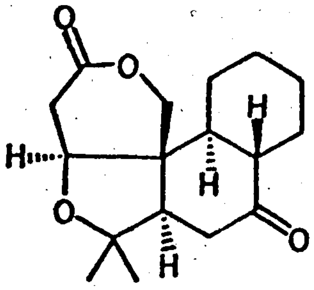
From the viewpoint of the synthetic chemist the limonin molecule can be seen to consist of two complex and highly functionalized ends (the AA' and DE ring systems) joined by a relatively simple *trans*-methyldecalone system (the BC ring system). A possible synthetic strategy would consist of the union of the two complex halves of the molecule followed by modification of the functional groups to give limonin (1). The primary objective of this work was the design of a synthesis of the AA'BC ring system of limonin with the model compound 8 as the target.



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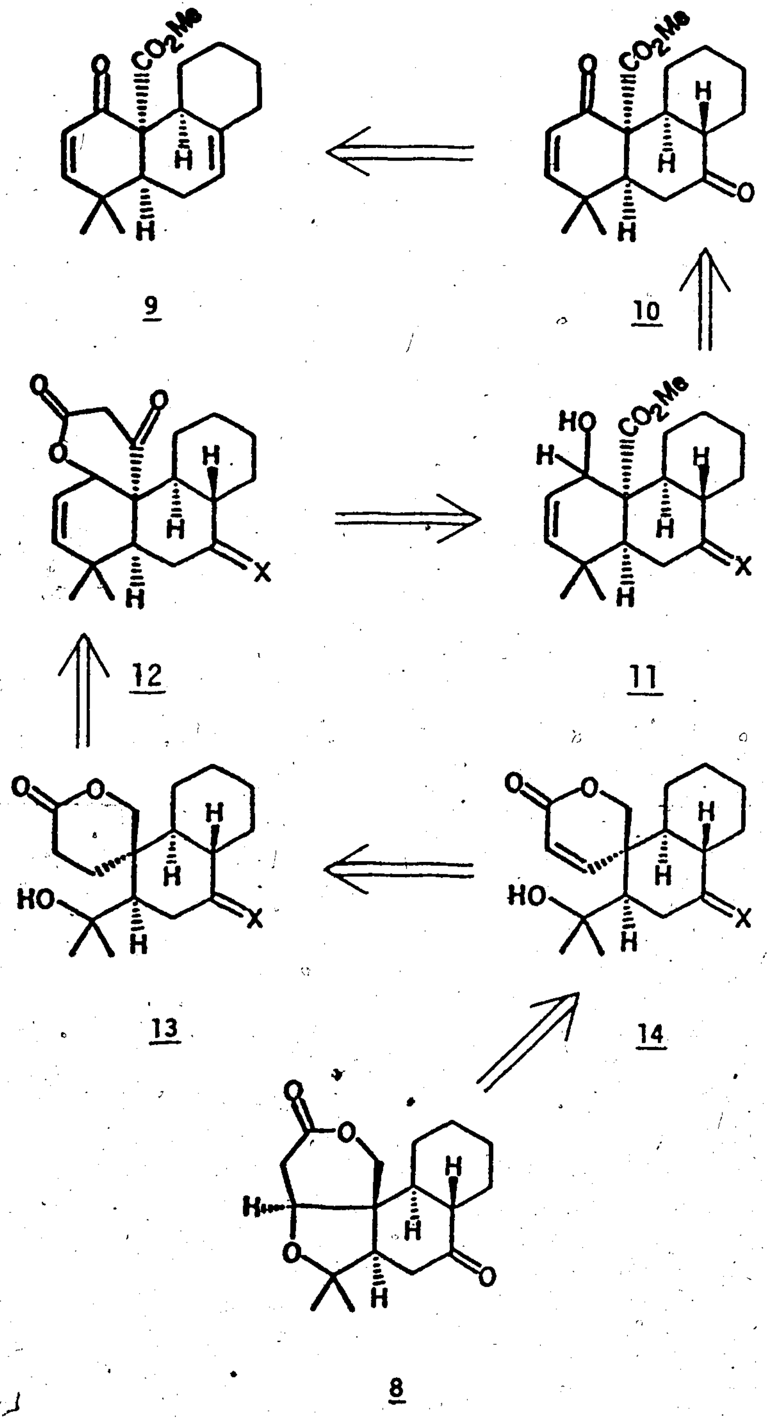
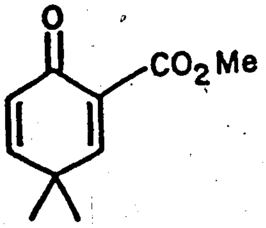
Retrosynthetic analysis showed that a ring system such as that of compound 8 might be accessible from the known Diels-Alder adduct 9 (Chapter 1) as shown in Scheme I. Conversion of the isolated double bond of 9 to a ketone would give 10. Protection of the saturated ketone of 10 followed by 1,2-reduction of the unsaturated ketone would give alcohol 11. An appropriate two carbon homologation of the side chain along with ring closure would give β-keto lactone 12. Selective removal of the ketone β to the lactone in 12 followed by degradation of the A' ring could give hydroxy lactone 13. Finally, introduction of a double bond into the A ring of 13 to give 14 followed by cyclization and deblocking of the saturated ketone could give the desired model compound 8.

Based on such a strategy it can be seen that the successful extension of this approach to the synthesis of limonin lies in the

Scheme I: The Synthetic Approach to the Limonin Model Compound <u>8</u>



choice of an appropriate Diels-Alder adduct as the key intermediate. Previous work (Chapter 1) has demonstrated that such adducts are easily generated from Lewis acid catalysed addition of dienes to dienone-ester 15. In the ideal case a diene such as 16 might be



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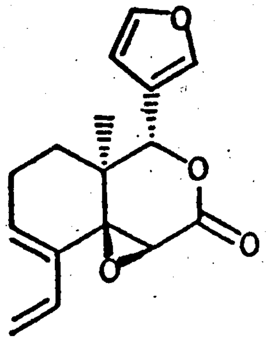

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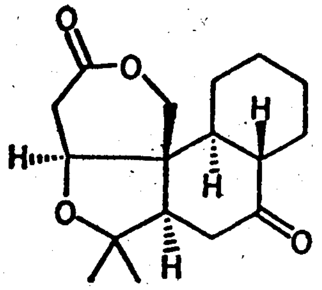
employed however in practice a suitably functionalized synthetic equivalent would almost certainly be required.

In this account the development of a highly efficient preparation of the key intermediate 9 and progress in its conversion to the model compound 8 are described.

Results and Discussion

Since the synthesis of limonin (1) via the scheme just described would proceed essentially via the linking of two moderately complex halves of the skeleton, it was important that the two halves be available in good yield and further that their linking by the Diels-Alder addition should proceed with relatively efficient use of both intermediates. It was desirable to examine these factors in the development of the synthesis of the model compound 8,



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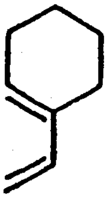
Two principal obstacles were encountered. Firstly, the published[9] preparation of the required diene 1-vinylcyclohexene (17)was reported to proceed in 87% yield by dehydration of 1-vinylcyclohexanol 18 with potassium bisulfate. In our hands however, a yield of only 24% was obtained. A report[10] that tertiary allylic alcohols could be dehydrated via the pyrolysis of their *p*-toluenesulfonylcarbamate derivatives to give dienes in good yield, offered an



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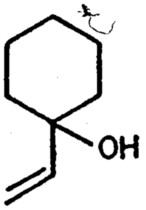

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alternate route to vinylcyclohexene (17). 1-Vinylcyclohexanol (18) was prepared by addition of vinyllithium (78% yield) or vinylmagnesium bromide (74% yield[11]) to cyclohexanone. Treatment of alcohol 18 with a slight excess of *p*-toluenesulfonyl isocyanate in benzene rapidly (1 hr.) gave the crude tosyl-carbamate 19 as a white powder* which was routinely used in crude form. Pyrolysis of 19 at ∿150°C and collection of the distillate in a water cooled trap gave pure 1-vinylcyclohexene (17) in 88% yield from alcohol 18.

The second obstacle to efficient generation of Diels-Alder adduct 9 was the observation that, under boron trifluoride etherate catalysis, the reaction of diene 17 with dienone-ester 15 required

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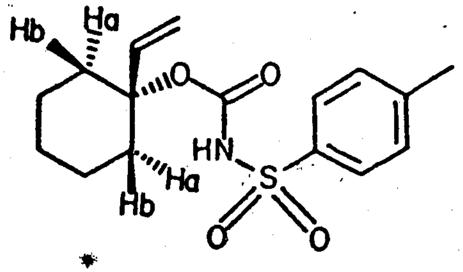
*Attempted recrystallization of this material from ether resulted in crystals (mp 48-59°C) which were found to be a 1:1 complex with ether. The crystals could be kept under vacuum for 24 hr. with no noticeable change in the nmr spectrum which showed signals due to diethyl ether (δ3.35 and δ1.12) superimposed on the spectrum of the carbamate 19.



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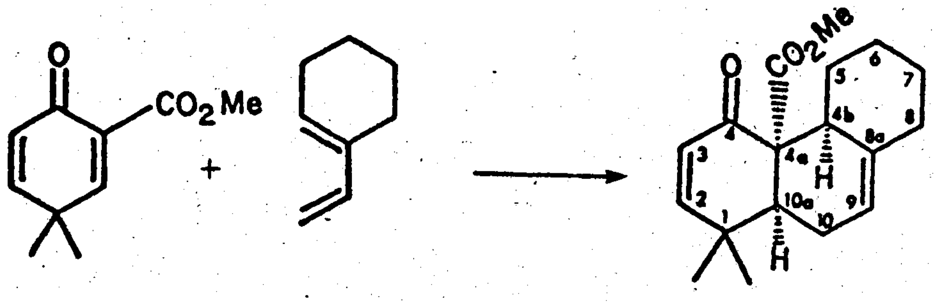
a large excess (20 equivalents) of 17 to give complete conversion of dienophile 15 within 2 1/2 days (Chapter 1). The observation that use of ferric chloride as a catalyst produced remarkably fast reaction times (Chapter 1) prompted its examination as a potential catalyst for achieving efficient addition of 17 to 15.

It was found that in ether solution under ferric chloride catalysis, Diels-Alder addition of 17 to 15 was complete within 45 min. using only two equivalents of diene to give keto-ester 9 as the only adduct in 72% yield. Complete conversions could be achieved using even



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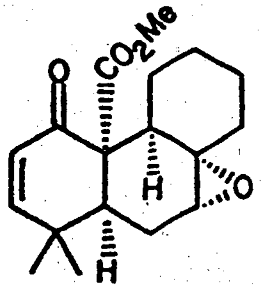
9

smaller excesses of the diene component at the expense of slightly lower overall yields. With an efficient preparation of the key intermediate 9 at hand, the conversion of 9 to the limonin AA'BC ring model compound 8 was examined.

Conversion of the double bond of 9 to a ketone proceeded via the epoxide 20. Treatment of 9 with *m*-chloroperbenzoic acid in methylene chloride at 0°C for 4 hr. gave epoxide 20* which could not be purified by silica gel column chromatography without hydrolylic cleavage of the epoxide ring**. For this reason the material was routinely used in crude form in the subsequent rearrangement reaction.



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Treatment of the crude epoxide 20 with boron trifluoride etherate[13,14] gave complete conversion to one principal product in 81% yield from keto-ester 9. The mass spectrum showed a molecular ion

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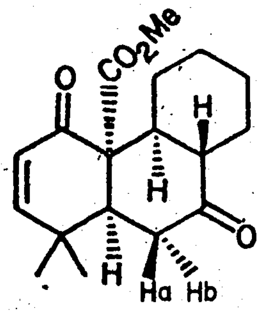
*The stereochemistry of the oxirane ring in 20 was assigned on the basis of attack from the less hindered face of the molecule.

**The opening of epoxide rings by silica gel to give carbonium ion rearrangement products has been reported by Dev[12].

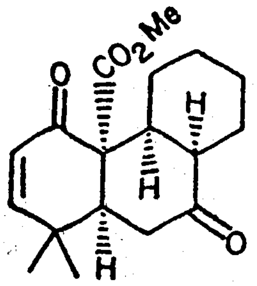
at m/e 304.1677 characteristic of the chemical formula $C_{18}H_{24}O_4$. The ir spectrum showed three carbonyl absorptions at 1730 (ester), 1710 (ketone) and 1685 cm^{-1} (enone). The nmr spectrum showed two coupled (J = 10 Hz) enone proton signals at δ6.18 and 5.86 and three methyl groups appeared as singlets at δ3.69, 1.14 and 1.10. These data were consistent with the assignment of structure <u>10</u> to the product.



<u>10</u>

The nmr spectrum of <u>10</u> provided a final and unambiguous proof of the *cis*-stereochemistry of the AB ring fusion in the starting Diels-Alder adduct <u>9</u>. As was discussed in Chapter 1, the assignment was made on the basis of the *cis*-principle of Diels-Alder addition and by analogy with several other rigorously proven cases of addition to dienone-ester <u>14</u>. The nmr signals of the protons at C-2 (δ6.18) and at C-10a (δ2.63) show a long range W-type coupling[15] of 2 Hz. As discussed in Chapter 1 the W-configuration required for such a coupling to occur can only be achieved in the *cis*-fused isomer and not in the *trans*-fused isomer. Thus it follows that the ketone <u>10</u>

as well as the keto-ester 9 from which it is derived must have a *cis* AB ring fusion. The assignment of the BC ring fusion stereochemistry as *trans* was made on the assumption of a stereospecific transfer[13,14] of the C-9 hydrogen to C-8a. This was supported by the observation that treatment of ketone 10 with sodium *t*-amylate at room temperature for 45 hr. gave quantitative recovery of unchanged ketone 10. Under such conditions the *cis-syn-cis* isomer 21



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would be expected to give the more stable* *cis-syn-trans* isomer 10.

Further elaboration of the molecule required protection of the newly formed saturated ketone. Thioketalization with 1,2-ethanedithiol catalysed by boron trifluoride etherate gave the expected product 22 in 82% yield (66% overall from keto-ester 9). In a simpler and more efficient preparation of 22 the crude epoxide 20 was treated first with boron trifluoride etherate for 5 min. and then 1,2-ethanedithiol was added to the solution at 0°C. The thioketal

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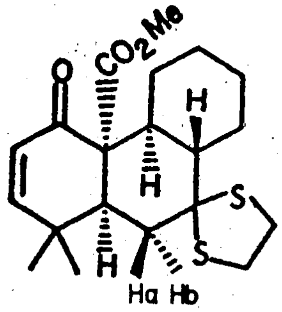
*This relative order of stability has been reported[16] in the case of perhydrophenanthrenes.



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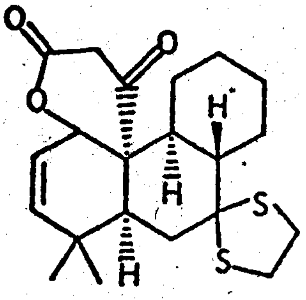
22 was obtained directly in 73% overall yield from keto-ester 9.

The conversion of thioketal 22 to the required β-keto lactone 23 could conceiveably be approached by two different routes using either



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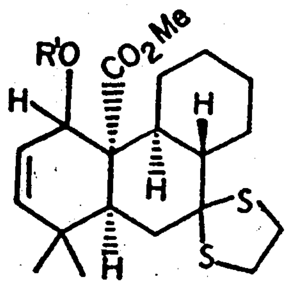
the ester side chain or the enone oxygen as the point of initial attachment of the group to be introduced. The route using the ester side chain would require selective 1,2-reduction of the enone and blocking of the resulting alcohol to give intermediate 24. Subsequently, addition of a synthetic equivalent of acetate anion 25 to the ester carbonyl followed by unmasking of the allylic alcohol



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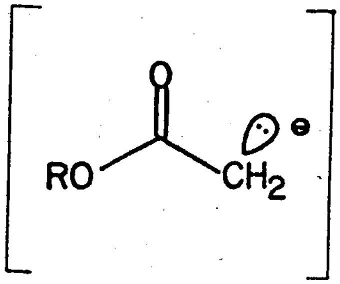

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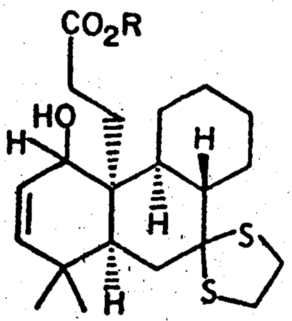
and, if necessary, the newly introduced side chain carboxyl function would give compound 26. Lactonization of 26 could give β-keto lactone



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23. A potentially simpler alternative approach to 23 using the enone oxygen as the site of initial attachment would also require selective 1,2-reduction of the enone and formation of an acetate derivative. Dieckman-type condensation of the acetate with the carbomethoxy side chain would give β-keto lactone 23.

To examine the latter approach, the enone system of 22 was subjected to a selective 1,2-reduction. Treatment with diisobutylaluminum hydride[17] in ether/toluene at 0°C* rapidly (10 min.) gave complete conversion to a chromatographically inseparable mixture (76% yield) of two principal products** in an $\sim$70:30 ratio by nmr integration. Routinely this mixture was carried on in the reaction sequence without further purification, however, for the purpose of characterization of the two products separation was possible by fractional crystallization from ether. By this method pure samples of each component were obtained.

The minor component gave a molecular ion at m/e 382.1631 in the mass spectrum indicating the chemical formula $C_{20}H_{30}O_3S_2$. The ir

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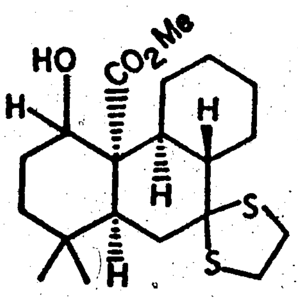
*The use of either higher or lower temperature resulted in an increased proportion of the 1,4-reduction product.

**The saturated alcohol 27 was also obtained in 3% yield.



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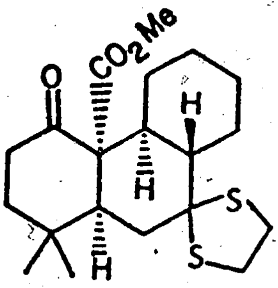
spectrum showed two carbonyl bands at 1739 (ester) and 1723 cm^{-1} (ketone). The nmr spectrum showed a four proton singlet at δ3.16 due to the thioketal group and methyl singlets at δ3.67, 1.11 and 0.98. These data indicated that the minor product was the saturated ketone 28 resulting from 1,4-reduction.



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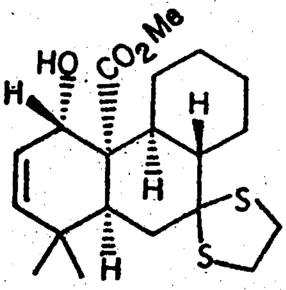
The major product gave a molecular ion at m/e 382.1640 in the mass spectrum ($C_{20}H_{30}O_3S_2$). The ir spectrum showed a hydroxyl absorption at 3505 cm^{-1} and an ester carbonyl at 1709 cm^{-1}. The nmr spectrum showed two coupled vinyl protons (J = 10 Hz) at δ5.46 and 5.17. The thioketal group gave a four proton singlet at δ3.18 and methyl groups appeared as singlets at δ3.62, 0.92 and 0.87. These data were consistent with the assignment of structure 29. The



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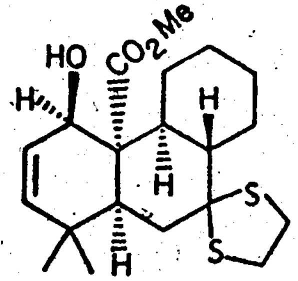
stereochemical assignment of the allylic hydroxyl group was supported by the nmr spectrum which showed the allylic proton as a broadened doublet (δ4.34) with a coupling constant of 12 Hz to the hydroxyl proton*. Examination of Dreiding models revealed that in 29 the dihedral angle between the allylic proton and the vinyl proton at C-2 (δ5.17) was ∿80°C which should account[18] for the observed negligible coupling. On the other hand, the epimeric alcohol 30 with a dihedral angle of ∿40° between these two protons would be expected to show a coupling constant of ∿5 Hz. The absence of such a coupling between those two protons in the nmr spectrum of the allylic alcohol obtained indicated the stereochemistry as shown in 29.



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Such a stereochemical outcome is in accordance with that predicted by the application of Baldwin's method of approach vector analysis[19] which takes into consideration steric interactions between the substituents of the substrate and the incoming hydride.

In an attempt to improve the ratio of 29:28 obtained by reduction

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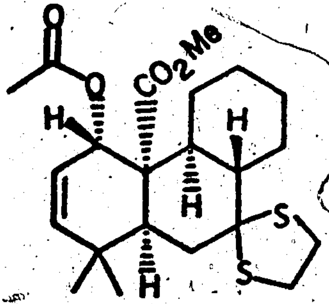
*This was confirmed by loss of the 12 Hz coupling on exchange with D_2O.

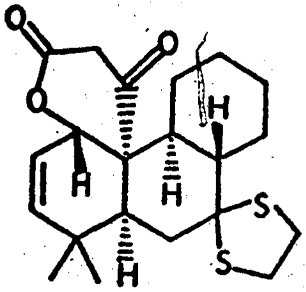
of enone 22, treatment with sodium borohydride/ceric chloride was examined. Such conditions have been reported[20] to produce almost exclusively the desired 1,2-reduction product. Unfortunately in this case no reduction was observed and the starting enone 22 was recovered quantitatively.

The 70:30 mixture of allylic alcohol 29 and saturated ketone 28 obtained by reduction with diisobutylaluminum hydride was treated with acetic anhydride in pyridine in the presence of a catalytic amount of 4-dimethylaminopyridine[21]. The saturated ketone 28 was recovered unchanged and was easily separated from the product by column chromatography on silica gel. The product, obtained in 70% yield, gave a molecular ion at m/e 424.1740 characteristic of the molecular formula $C_{22}H_{32}O_4S_2$. The ir spectrum showed ester carbonyl absorptions at 1744 and 1732 cm^{-1}. The nmr spectrum showed two vinyl protons at δ5.28 and 5.16, a thioketal group as a four proton singlet at δ3.19, and methyl groups as singlets at δ3.60 (ester), 2.00 (acetyl), 0.96 and 0.89. These data indicated the structure of the product as that defined by structure 31.

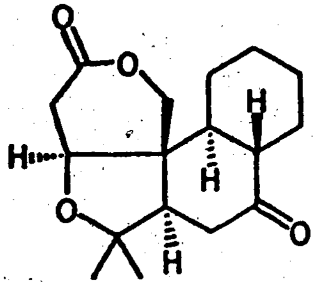


31

Methods are currently under study for the condensation of acetate 31 to the β-keto lactone 23 which could then be converted to the desired model compound 8 in accordance with the synthetic scheme outlined previously.



23



8

Experimental

General

For general remarks see Chapter 1 of this thesis.

Materials

Benzene was distilled over lithium aluminum hydride. Pyridine was distilled over barium oxide and stored over potassium hydroxide pellets. Boron trifluoride etherate was distilled over calcium hydride according to the procedure of Brown[22,23]. Nitrogen was passed through a purification train of Fieser's solution[23], saturated aqueous lead acetate, concentrated sulfuric acid and potassium hydroxide pellets. Dienone-ester 15 was prepared according to the procedure described in Chapter 1 of this thesis.

1-Vinylcyclohexanol (18)

A 1.40 N solution of vinyl lithium in tetrahydrofuran (300 ml, 0.42 mmol of vinyl lithium) was added to anhydrous ether (700 ml) by forced siphon[24] at 0°C under an atmosphere of nitrogen. A solution of cyclohexanone (39.3, 0.40 mmol) in anhydrous ether (300 ml) was added to the stirred solution dropwise over 90 min. After stirring for 30 min. the reaction mixture was poured into ice-cold saturated aqueous ammonium chloride with vigorous stirring. The resulting mixture was extracted with ether and the extracts were washed with water, dried (sodium sulfate), filtered, and concentrated. Distillation of the residue gave pure alcohol <u>18</u> (44.35 g, 78% yield) as a colourless oil: bp 67-69°C/16 Torr; nmr 5.87 (dd, 1H, J = 18, J' = 11 Hz, $-C\underline{H}{=}CH_2$), 5.14 (dd, 1H, J = 18, J' = 2 Hz, $-CH{=}CH\text{-}\underline{H}$ (Z)), 4.90 (d, 1H, J = 11, J' = 2 Hz, $-CH{=}CH\text{-}\underline{H}$ (E)), 1.64 (s, 1H, $-O\underline{H}$), and 1.47 (br. s, 10H, 5x $-CH_2-$); ir (neat) 3600 (OH, free), 3390 (OH, H-bonded), 3080 ($-CH{=}CH_2$), 1640 (C=C), 995 and 970 cm^{-1} ($-CH{=}CH_2$).

1-(*p*-Toluenesulfonylcarbamoyl)-1-vinylcyclohexane (<u>19</u>)

Alcohol <u>18</u> (1.22 g, 9.71 mmol) was dissolved in benzene (10 ml, distilled over lithium aluminum hydride) and a solution of *p*-toluenesulfonylisocyanate (2.11 g, 10.6 mmol) in benzene (5.0 ml) was added with stirring. After 1 hr. a small amount of water (~100 µl) was added to destroy excess isocyanate and the solution was diluted with ether (~5 ml), dried, filtered and concentrated under vacuum at room temperature. The crude carbamate <u>19</u> (3.95 g, 126% yield) thus obtained as powdery crystals[*] was contaminated with *p*-toluenesulfonamide. Column chromatography of a portion (495 mg) of this crude product on silica gel, eluting with 25-50% ether in petroleum ether, gave pure

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[*] One recrystallization of the crude carbamate <u>19</u> (900 mg) from ether gave colourless crystals (mp. 48-59°C, 350 mg) which were identified as the mono-etherate complex of <u>19</u> by their nmr spectrum. In addition to signals due to the carbamate <u>18</u> two signals due to diethyl ether were observed at δ3.35 (q, 4H, J = 7 Hz, 2x $-OCH_2-$), and δ1.12 (t, 6H, J = 7 Hz, 2x $-CH_3$).

carbamate 19 (230 mg, 59% yield from alcohol 18) as a colourless viscous oil: nmr δ8.30 (s, 1H, $-NH-$), 7.83 (d, 2H, J = 8 Hz, 2x $-SO_2-\overset{|}{C}=CH-$), 7.24 (d, 2H, J = 8 Hz, 2x $CH_3-\overset{|}{C}=C\underline{H}-$), 5.83 (dd, 1H, J = 18, J' = 11 Hz, $-C\underline{H}=CH_2$), 4.96 (d, 1H, J = 11 Hz, $-CH=CH-\underline{H}$ (E)), 4.91 (d, 1H, J = 18 Hz, $-CH=CH-\underline{H}$ (Z)), 2.43 (s, 3H, $-CH_3$), 2.10 (br. s, 2H, 2x $-O-\overset{|}{\underset{|}{C}}-\overset{|}{C}H-\underline{H}a$), and 1.50 (br. s, 8H, 3x $-CH_2-$ and 2x $-O-\overset{|}{\underset{|}{C}}-\overset{|}{\underset{|}{C}}H-\underline{H}b$); ir (neat) 1780 (C=O), 1588, 1483 (C=C, aromatic), 1335 ($-SO_2-\overset{|}{N}-$), and 1145 cm^{-1} ($-SO_2-$); ms (NH_3 chemical ionisation) parent peak 341 ($M + NH_4^+$). Anal. Calcd. for $C_{16}H_{21}NO_4S$: C 59.42, H 6.54, N 4.33, S 9.91; Found: C 59.21, H 6.83, N 3.96, S 9.55.

1-Vinylcyclohexene (17)

Crude carbamate 19 (3.38 g, 10.4 mmol) was heated in a Kugelrohr apparatus to ~150°C and the distillate was collected in a water-cooled outer trap for 1 hr. The distillate was found to be pure vinylcyclohexene 17 (790 mg, 87% from alcohol 18) as a colourless liquid: nmr δ6.21 (dd, 1H, J = 18, J' = 10 Hz, $-C\underline{H}=CH_2$), 5.65 (br. s, 1H, $-\overset{|}{C}=CH-$), 4.93 (d, 1H, J = 18 Hz, $-CH=CH-\underline{H}$ (Z)), 4.80 (d, 1H, J = 10 Hz, $-CH=CH-\underline{H}$ (E)), 2.02 (m, 4H, $-C\underline{H}_2-\overset{|}{C}=CH-C\underline{H}_2-$), and 1.64 (m, 4H, $-C\underline{H}_2-C\underline{H}_2$); ir (neat) 3090 ($-CH=CH_2$), 3030 ($-CH=CH_2$), 1645 (C=C) 995 and 905 cm^{-1} ($-CH=CH_2$).

4aα-Carbomethoxy-1,1-dimethyl-4a,4bα,5,6,7,8,10,10aα-octahydro-4(1_H_)-phenanthrenone (_9_)*

Dienone-ester _15_ (1.05 g, 5.84 mmol) was dissolved in ether (50 ml, distilled over lithium aluminum hydride) under an atmosphere of nitrogen. Ferric chloride (473 mg, 2.92 mmol) was added with stirring followed rapidly by 1-vinylcyclohexene (1.26 g, 11.7 mmol). After 45 min., saturated aqueous sodium bicarbonate (10 ml) was added and the resulting mixture was extracted with ether. The extracts were washed with water, dried, filtered and concentrated. Column chromatography of the residue on silica gel, eluting with 7% ether in petroleum ether, gave pure adduct _9_ (1.20 g, 72% yield).

Spectral data for adduct _9_ have already been reported in Chapter 1 of this thesis.

4aα-Carbomethoxy-4,4-dimethyl-8aα,9α-epoxy-4a,4bα,5,6,7,8,9,10,10aα-decahydro-4(1_H_)-phenanthrenone (_20_)

Adduct _9_ (900 mg, 3.12 mmol) was dissolved in methylene chloride and cooled to 0°C under an atmosphere of nitrogen. Purified[25] *m*-chloroperbenzoic acid (1.08 g, 6.25 mmol) was added slowly to the stirred solution. After 225 min. a 10% aqueous solution of sodium

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*The stereochemical designations used in this and all other chemical names in this section denote _relative_ stereochemistry. All compounds used and obtained were racemic.

sulfite (10 ml) was added and the resulting mixture was extracted with ether. The extracts were washed with ice-cold saturated aqueous sodium bicarbonate and water, dried, filtered and concentrated to give crude epoxide 20 (1.08 g, 114% crude yield) as a viscous oil. The crude material was used directly in subsequent reactions. Crude epoxide 20 showed the following spectral data: nmr δ6.20 (dd, 1H, J = 11, J' = 1.5 Hz, $-C\underline{H}=CH-CO-$), 5.80 (d, 1H, J = 11 Hz, $-CH=C\underline{H}-CO-$), 3.63 (s, 3H, $-O-CH_3$), 2.88 (m, 1H, $-\overset{|}{C}H-O-$), and 1.10 (s, 6H, 2x $-CH_3$); ir (CCl_4), 1727 (C=O, ester), 1687 (C=O, enone), 1374 (CH_3), 909 and 765 cm^{-1} (epoxide); ms M^+ 304.1671 (calcd. for $C_{18}H_{24}O_4$: 304.1674).

4aα-Carbomethoxy-1,1-dimethyl-4a,4bα,5,6,7,8,10,10aα-octahydro-4,9(1H,-8aβ H)-phenanthrenedione (10)

Crude epoxide 20 (375 mg, 1.23 mmol) was dissolved in dry benzene (20 ml). Boron trifluoride etherate (151 μl, 175 mg, 1.23 mmol) was added to the stirred solution. After 5 min. saturated aqueous sodium bicarbonate (3 ml) was added and the resulting mixture was extracted with methylene chloride. The extracts were washed with water, dried, filtered and concentrated. Column chromatography of the residue on silica gel, eluting with 14-40% ether in petroleum ether, gave crystalline diketo-ester 10 (256 mg, 81% yield from adduct 9). One recrystallization from petroleum ether gave pure white crystals of diketo-ester 10: mp 102-105°C; nmr δ6.18 (dd, 1H, J = 10, J' = 2 Hz, $-C\underline{H}=CH-CO-$), 5.86 (d, 1H, J = 10 Hz, $-CH=C\underline{H}-CO-$), 3.69 (s, 3H, $-O-CH_3$), 2.63 (ddd, 1H, J = 15, J' - 4, J" = 2 Hz, C-10a H), 2.48 (d, 1H, J = 15 Hz, C-10 Ha), 2.41 (d, 1H, J = 4 Hz, C-10 Hb), 1.14 (s, 3H, $-CH_3$), and 1.10 (s, 3H, $-CH_3$); ir 1730 (C=O, ester), 1710 (C=O, ketone), 1685 (C=O, enone), and 1386 cm^{-1} (CH_3); ms M^+ 304.1677 (calcd. for $C_{18}H_{24}O_4$: 304.1674). Anal. Calcd. for $C_{18}H_{24}O_4$: C 71.03, H 7.95; Found: C 71.11, H 8.11.

Attempted Base Catalysed Epimerization of Ketone 10

Ketone 10 (56 mg, 0.18 mmol) was dissolved in 1,2-dimethoxyethane (5 ml, freshly distilled over lithium aluminum hydride) and sodium hydride (8 mg, 0.18 mmol, washed with ether) was added followed by *t*-amyl alcohol (16 mg, 0.18 mmol). After 45 hr. the mixture was poured into saturated aqueous ammonium chloride and extracted with methylene chloride. The extracts were washed with water, dried, filtered and concentrated. The product (57 mg, 100% recovery) was identical by nmr analysis with pure starting ketone 10.

4aα-Carbomethoxy-1,1-dimethyl-9,9-ethylenedithio-4a,4bα,5,6,7,8,8aβ,9,10,10aα-decahydro-4(1H)-phenanthrenone (22)

a. From Diketone (10)

Diketo-ester 10 (222 mg, 0.73 mmol) was dissolved in methylene chloride (3 ml) and the solution was cooled to 0°C. Ethane 1,2-

dithiol (344 mg, 3.65 mmol) was added followed by boron trifluoride etherate (103 mg, 0.73 mmol). After stirring for 13 min. saturated aqueous sodium bicarbonate (1 ml) was added and the resulting mixture was extracted with methylene chloride. The extracts were washed with ice-cold 1.0 N aqueous sodium hydroxide and water, dried, filtered and concentrated. Column chromatography of the residue on silica gel, eluting with 4-8% ether in petroleum ether, gave thioketal 22 (229 mg, 82% yield, 66% yield from adduct 9) which crystallized on standing. One recrystallization from ether gave white crystals of pure thioketal 22 (59 mg): mp 148-151°C; nmr δ6.10 (dd, 1H, J = 10, J' = 2 Hz, $-C\underline{H}{=}CH-CO-$), 5.75 (d, 1H, J = 10 Hz, $-CH{=}C\underline{H}-CO-$), 3.64 (s, 3H, $-O-CH_3$), 3.19 (s, 4H, $-S-C\underline{H}_2-C\underline{H}_2-S-$), 2.41 (ddd, 1H, J = 14, J' = 3, J" = 2 Hz, C-10a H), 2.29 (d, 1H, J = 14 Hz, C-10 Ha), 2.24 (d, 1H, J = 3 Hz, C-10 Hb), and 1.08 (s, 6H, 2x $-CH_3$); ir 1728 (C=O, ester), 1684 (C=O, enone), 1371 and 1365 cm^{-1} (CH_3); ms M^+ 380.1471 (calcd. for $C_{20}H_{28}O_3S_2$: 380.1480). Anal. Calcd. for $C_{20}H_{28}O_3S_2$: C 63.12, H 7.42, S 16.85; Found: C 62.94, H 7.57, S 16.84.

b. From Epoxide 20

Crude epoxide 20 (347 mg, 1.14 mmol) was dissolved in dry benzene (20 ml). Boron trifluoride etherate (162 mg, 1.14 mmol) was added to the stirred solution. After 5 min. the solution was cooled to 5°C over ∿5 min. and ethane 1,2-ethanedithiol (210 mg, 2.28 mmol) was added. After stirring for 14 min. saturated aqueous sodium bicarbonate (2 ml) was added and the resulting mixture was extracted with methylene chloride. The extracts were washed with ice-cold 1.0 N aqueous sodium hydroxide and water, dried, filtered and concentrated. Column chromatography of the residue on silica gel, eluting with 10% ether in petroleum ether, gave thioketal 22 (276 mg, 73% yield from adduct 9).

4aα-Carbomethoxy-1,1-dimethyl-9,9-ethylenedithio-4aαhydroxy-1,4,4a,4bα,5,6,7,8,8aβ,9,10,10aα-dodecahydrophenanthrene (29), 4aα-Carbomethoxy-1,1-dimethyl-9,9-ethylenedithio-4a,4bα,5,6,7,8,8aβ,9,10,10aα-decahydro-4(1H)-phenanthrenone (28) and 4aα-Carbomethoxy-1,1-dimethyl-9,9-ethylenedithio-4aα-hydroxy-1,2,3,4,4a,4bα,5,6,7,8,8aβ,9,10,10aα-tetradecahydrophenanthrene (27)

Thioketal 22 (237 mg, 0.62 mmol) was dissolved in anhydrous ether (7 ml) under an atmosphere of nitrogen. The solution was cooled to 0°C and a 25% solution of diisobutylaluminum hydride in toluene (1.41 ml, 2.49 mmol) was added. After stirring for 10 min., water (1 ml) was added and the mixture was extracted with methylene chloride. The extracts were washed with water, dried, filtered and concentrated. Column chromatography on silica gel, eluting with 5-10% ether in petroleum ether gave an ~70:30 mixture (182 mg, 76% yield) of allylic alcohol 29 and saturated ketone 28. Further elution with 10% ether in petroleum ether gave saturated alcohol 27 (7 mg, 3% yield): nmr δ4.45 (br. s, 1H, $-OH$), 3.59 (s, 4H total, $-O-CH_3$

and $-\overset{|}{C}\underline{H}-OH$), 3.16 (s, 4H, $-S-C\underline{H}_2-C\underline{H}_2-S-$), 0.92 (s, 3H, $-CH_3$), and 0.79 (s, 3H, $-CH_3$); ir 3526 (OH), 1699 (C=O), and 1379 cm^{-1} (CH_3); ms M$^+$ 384.1792 (calcd. for $C_{20}H_{32}O_3S_2$: 384.1792).

Fractional crystallization of the mixture of 29 and 28 from ether gave pure samples of allylic alcohol 29 and saturated ketone 28. Alcohol 29 showed the following data: mp 153-5°C; nmr δ5.46 (dd, 1H, J = 10, J' = 2 Hz, $-\underline{H}C=CH-\overset{|}{C}H-OH$), 5.17 (dm, 1H, J = 10 Hz, $=C\underline{H}-\overset{|}{C}H-OH$), 4.34 (dm, 1H, J = 12 Hz, $-\overset{|}{C}\underline{H}-OH$), 3.76 (d, 1H, J = 12 Hz, $-\overset{|}{C}H-O\underline{H}$), 3.62 (s, 3H, $-O-CH_3$), 3.18 (s, 4H, $-S-C\underline{H}_2-C\underline{H}_2-S-$), 0.92 (s, 3H, $-CH_3$), and 0.87 (s, 3H, $-CH_3$); ir 3505 (OH) and 1709 cm^{-1} (C=O); ms M$^+$ 382.1640 (calcd. for $C_{20}H_{30}O_3S_2$: 382.1636). *Anal.* Calcd. for $C_{20}H_{30}O_3S_2$: C 62.79, H 7.90, S 16.76; Found: C 62.89, H 7.99, S 16.74. Ketone 28 showed the following data: mp 137-140°C; nmr δ3.67 (s, 3H, $-O-CH_3$), 3.16 (s, 4H, $-S-C\underline{H}_2-C\underline{H}_2-S-$), 2.92 (ddd, 1H, J = J' = 14, J" = 7 Hz, $-CO-CH\underline{H}-$), 1.11 (s, 3H, $-CH_3$), and 0.98 (s, 3H, $-CH_3$); ir 1739 (ester C=O), 1723 (ketone C=O), 1390 and 1368 cm^{-1} (CH_3); ms M$^+$ 382.1631 (calcd. for $C_{20}H_{30}O_3S_2$: 382.1636). *Anal.* Calcd. for $C_{20}H_{30}O_3S_2$: C 62.79, H 7.90, S 16.76; Found: C 62.54, H 7.83, S 16.70.

4α-Acetoxy-4aα-carbomethoxy-1,1-dimethyl-9,9-ethylenedithio-1,4,4a,4bα,5,6,7,8,8aβ,9,10,10aα-docecahydrophenanthrene (31)

A 67:33 mixture of allylic alcohol 29 and ketone 28 (330 mg, 0.86 mmol) was dissolved in pyridine (5 ml) and 4-dimethylaminopyridine[21]

(10 mg) was added followed by acetic anhydride (881 mg, 8.6 mmol). After stirring for 50 hr. the mixture was poured into cold aqueous 5% hydrochloric acid and extracted with ether. The extracts were washed with aqueous 5% hydrochloric acid and water, dried, filtered and concentrated. Column chromatography of the residue on silica gel, eluting with 5-7% ether in petroleum ether, gave ketone 28 (96 mg, 29% of starting mixture, assumed 100% recovery of 28). Further elution with 10-25% ether in petroleum ether gave acetate 31 (182 mg, 70% yield based on recovered ketone 28) which crystallized on standing. One recrystallization from petroleum ether gave pure acetate 31: mp 121-124°C; nmr δ5.67 (s, 1H, $-\overset{|}{\mathrm{C}}\underline{\mathrm{H}}-\mathrm{OAc}$), 5.28, 5.16 (both d, 2H total, both J = 11 Hz, $-\mathrm{HC{=}CH}-$), 3.60 (s, 3H, $-\mathrm{O}-\mathrm{CH_3}$), 3.19 (s, 4H, $-\mathrm{S}-\mathrm{C\underline{H}_2}-\mathrm{C\underline{H}_2}-\mathrm{S}-$), 2.00 (s, 3H, $\mathrm{C\underline{H}_3}-\mathrm{CO_2}-$), 0.96 (s, 3H, $-\mathrm{CH_3}$), and 0.89 (s, 3H, $-\mathrm{CH_3}$); ir 1744, 1734 (ester C=O) and 1377 $\mathrm{cm^{-1}}$ ($\mathrm{CH_3}$); ms $\mathrm{M^+}$ 424.1740 (calcd. for $\mathrm{C_{22}H_{32}O_4S_2}$: 424.1742). Anal. Calcd. for $\mathrm{C_{22}H_{32}O_4S_2}$: C 62.23; H 7.60, S 15.10; Found: C 62.18, H 7.78, S 15.13.

References

1. Bernays, Ann., 40, 317 (1841).
2. D.H.R. Barton, S.K. Pradham, S. Sternhell, and J.F. Templeton, J. Chem. Soc., 255 (1961).
3. D. Arigoni, D.H.R. Barton, E.J. Corey, O. Jeger, L. Cagliotti, S. Dev, P.G. Ferrini, E.R. Glazier, A. Melera, S. Pradham, K. Schaffner, S. Sternhell, J.F. Templeton, and S. Tobinga, Experientia, 16, 49 (1960).
4. A. Melera, K. Schaffner, D. Arigoni, and O. Jeger, Helv. Chim. Acta, 40, 1420 (1957).
5. S. Arnott, A.W. Davie, J.M. Robertson, G.A. Sim, and D.G. Watson, Experientia, 16, 49 (1960).
6. S. Arnott, A.W. Davie, J.M. Robertson, G.A. Sim, and D.G. Watson, J. Chem. Soc., 4183 (1961).
7. H.R. Schlatter, C. Luthy, and W. Graf, Helv. Chim. Acta, 57, 1044 (1974).
8. C. Luthy, H.R. Schlatter, and W. Graf, Helv. Chim. Acta, 57, 1060 (1974).
9. P.A. Robins and J. Walker, J. Chem. Soc., 642 (1952).
10. Z. Valenta, personal communication.
11. H.J. Liu and I.V. Oppong, unpublished results.
12. V.S. Joshi, N.P. Damodaran, and S. Dev, Tetrahedron, 27, 475 (1971).
13. H.B. Henbest and T.I. Wrigley, J. Chem. Soc. 4596 (1957).

14. C.W. Shoppee, M.E.H. Howden, P.W. Killick, and G.H.R. Summers, J. Chem. Soc., 630 (1959).

15. L.M. Jackman and S. Sternhell, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry", 2nd. ed., Pergamon, Oxford, 1969.

16. E.L. Eliel, "Stereochemistry of Carbon Compounds", McGraw Hill, New York, 1962.

17. K.E. Wilson, R.T. Seidner, and S. Masamune, J. Chem. Soc., Chem. Comm., 213 (1970).

18. R.M. Silverstein and G.C. Bassler, "Spectrophotometric Identification of Organic Compounds", 2nd ed., Wiley, New York, 1967.

19. J.E. Baldwin, J. Chem. Soc., 738 (1976).

20. J.L. Luche, J. Amer. Chem. Soc., <u>100</u>, 2226 (1978).

21. W. Steglich and G. Hofle, Angew. Chem. Int. Ed. Engl., <u>8</u>, 981 (1969).

22. G. Zweifel and H.C. Brown, Organic Reactions, <u>13</u>, 28 (1963).

23. L.F. Fieser and M. Fieser, "Reagents for Organic Synthesis, Vol. 1, Wiley, New York, 1967.

24. C.F. Lane and G.W. Kramer, Aldrichimica Acta, <u>10</u>, 11 (1977).

25. N.N. Schwartz and J.H. Blumbergs, J. Org. Chem., <u>29</u>, 1976 (1964).