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Title: The Photochemistry of Some Insect Juvenile Hormone Analogs

Abstract approved: Redacted for Privacy

Dr. Peter K. Freeman

The photochemistry of some analogs of insect growth regulators (IGR's) was studied. Methyl geranate, 71, was synthesized and the mechanisms of its photochemical reaction pathways were studied by a variety of techniques. Direct irradiation of 71 in ether leads to the formation of five new products: 98, the product of a [1,3] sigmatropic shift; 72, a bicyclo[2.1.1]hexane derivative; 73, a cylclopentane derivative; 100, the product of in-chain deconjugation to the Z isomer; and 97, the product of isomerization about the C-2 bond. Irradiation in the presence of propiophenone as a triplet sensitizer lead to the formation of only 72, 73 and 97, identifying them as arising from the triplet excited state. Irradiation of 71 in ether with varying amounts of base lead to the formation of (in addition to products already mentioned) 99 and 100, the other two possible deconjugation products. Examination of Scheme 29 leads to the derivation of the kinetic rate expressions in Scheme 31, and plotting the ratios of 99/73, 100/73 and 101/73 yields values for the relative rate of [1,5] sigmatropic shift of hydrogen from a photodienol species

(119, 121, 123) to regenerate starting esters (71, 97) rather than going on to deconjugation products (99, 100, 101). It was found that the relative rates of sigmatropic shift for 119 and 123 were nearly identical but 121 was about 75 times slower. This decrease in the relative rate for 121 is ascribed to the extra steric repulsion in 121, causing it to adopt the unreactive s-trans conformation and thus slowing the reaction.

Insect juvenile hormone, 74, was synthesized and irradiated in ether and was found to undergo photochemical processes similar to that of 71. The primary photoprocess is isomerizatrion about the C-2 and C-6 double bonds. Isomerization about the C-6 bond was unexpected and indicated the intermediacy of an exciplex.

To study the role of exciplexes in the E/Z isomerizartion of isolated double bonds in the juvenile hormone, 74, the unsymmetrically terminated analog 92 and the dihydro analog 93 were synthesized.

Irradiation of 92 and 93 in solvents of varying polarity (E_T) lead to an increase of the quantum yield of E/Z isomerization for both 92 and 93, indicating the intermediacy of an intermolecular exciplex. to study the role of intramolecular exciplexes 92 and 93 were irradiated in ether at increasing dilution (0.1 M - 0.0008 M). It was found that the intermolecular exciplex is the major contributor in the concentration range studied without any evidence for an intramolecular exciplex.

The Photochemistry of Some Insect Juvenile Hormone Analogs

by

Lorenz Siggel

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Typed by Lorenz Siggel

This thesis is dedicated to the memory of my sister:

Angelika Siggel-Viljoen

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"What does not kill us,
Makes us stronger."
F. Nietsche

In looking back over the five years that I have spent at OSU I've come to realize that there are more people to whom I owe thanks than I can possibly list individually. However, here is a short list of some of the people who have made this thesis possible.

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Many friends and colleagues too numerous to mention by name: I learned more useful techniques from other grad students and post-docs than I can remember. The friends come and go but the memories linger (at least until total senility stikes).

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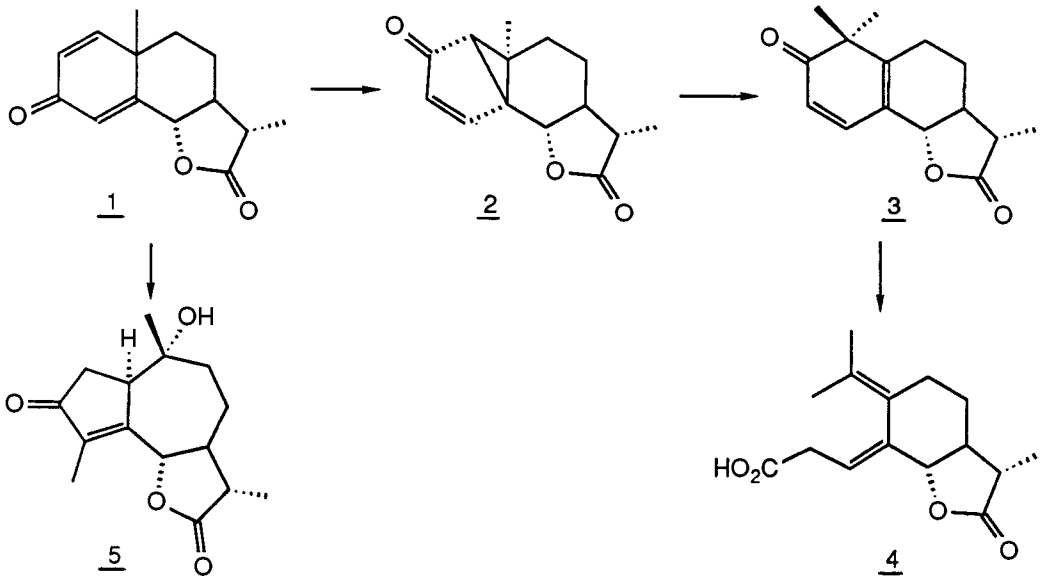
THE PHOTOCHEMISTRY OF SOME INSECT JUVENILE HORMONE ANALOGS

INTRODUCTION

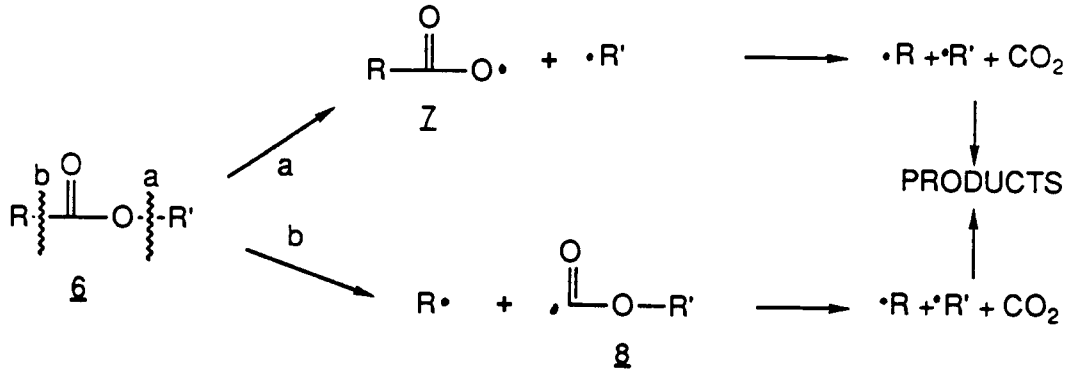
The history of the photochemistry of α,β-unsaturated carbonyl compounds goes back to at least 1830 when Kahler[1] observed a photochemical transformation of α-santonin, 1, but it took an additional 135 years for chemists to unambiguously assign structures to the reaction products, Scheme 1.[2] Since Kahlers time, thousands of papers on the photochemical reactions of α,β-unsaturated aldehydes and ketones have appeared in the scientific literature, but the literature on α,β-unsaturated ester photochemistry is sparse. [3]

Scheme 1

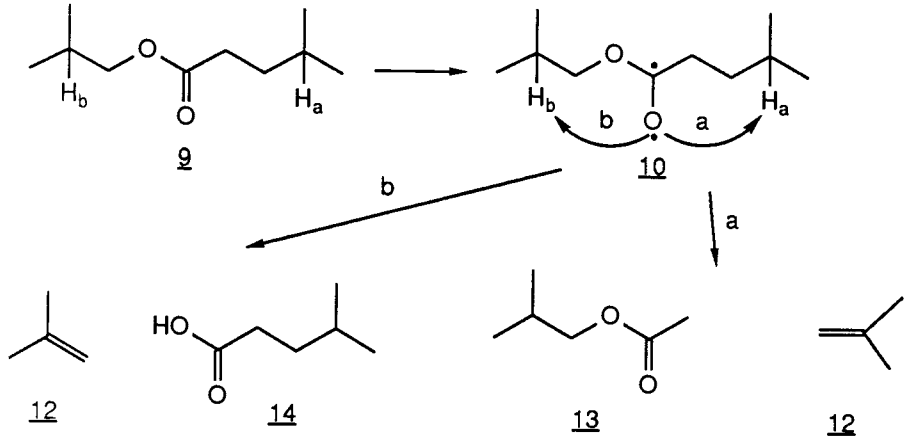


The primary photoprocesses of saturated carboxylic acids or esters are cleavage reactions, Scheme 2. These cleavage reactions can be categorized as Norrish type I, Scheme 2, or Norrish type II, Scheme 3, reactions in direct analogy to the photocleavage reactions of aldehydes and ketones.[3] Type I cleavage results in decarboxylation of the acid via free radical intermediates 7 or 8. The direction, path a or b, and rates of these type I cleavage reactions are quite dependent on the ability of the groups on the acid to stabilize the intermediate radicals. Type II cleavage is the result of intramolecular hydrogen atom abstraction, via a six membered ring transition state, Scheme 3. In the example given ester 9 upon absorption of light is promoted to the excited state 10. Abstraction of H_a by oxygen, path a, results in formation of olefin 12 and, after proton transfer, ester 13. Abstraction of H_b, path b, results in the formation of olefin 12 and acid 14.

Scheme 2

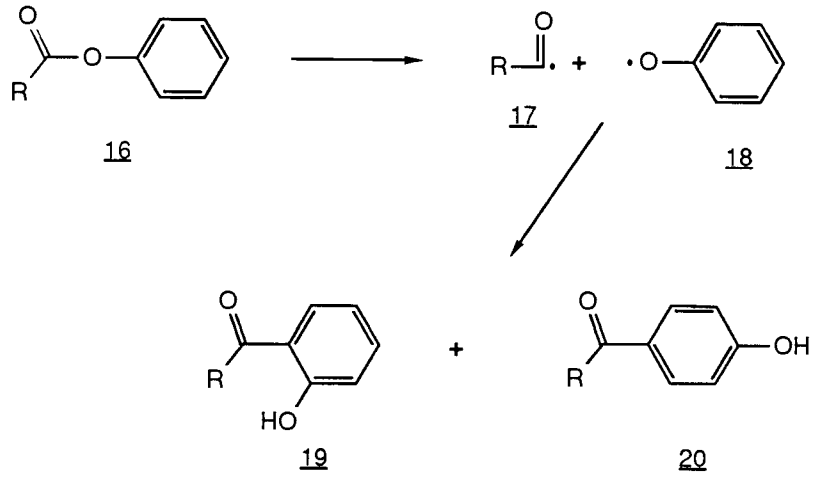


Scheme 3



Aryl esters, such as 16, can also undergo a rearrangement reaction ("photo Fries rearrangement") when irradiated with ultraviolet (UV) light, Scheme 4.[4] Absorption of light, followed by α-cleavage to form radicals 17 and 18 and recombination of the acyl radical at the ortho or para positions of the phenoxy radical yields, after tautomerization, ketones 19 and 20. The free radical pathway of this reaction has been established by Kalmus and Hercules[5] by direct observation of phenoxy radicals in laser flash photolysis experiments.

Scheme 4

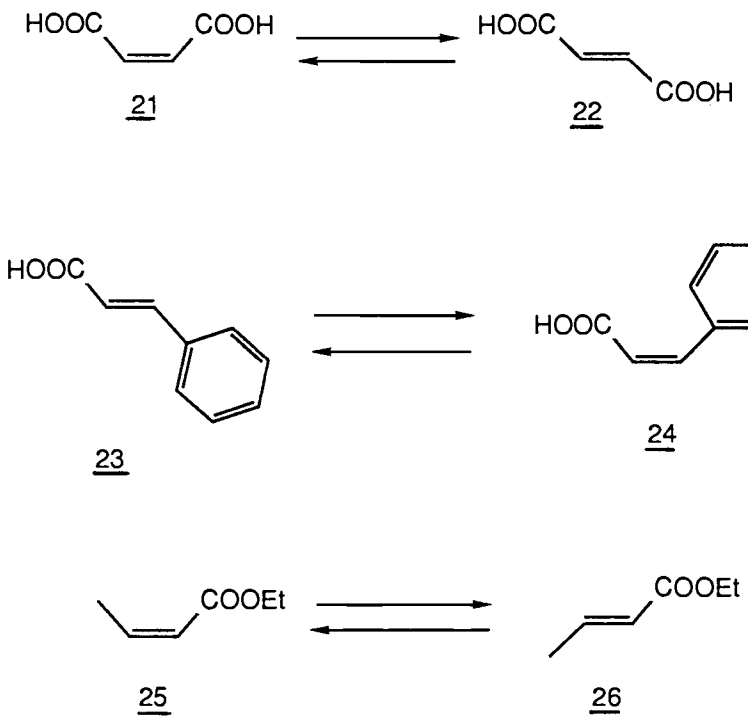


In contrast to their saturated counterparts, α,β-unsaturated acids and esters generally do not undergo cleavage reactions when irradiated with UV light. Olson and Hudson[6] have shown that maleic acid, 21, and trans-cinnamic acid, 23, both form a cis/trans photoequilibrium mixture when irradiated with an unfiltered mercury arc lamp, but they detected no products resulting from decarboxylation. Irradiation of cis-ethyl crotonate, 25, leads only to a photoequilibrium mixture of the cis/trans isomers with no products of decarboxylation detected, Scheme 5.

This vastly different behavior to decarboxylation between saturated and unsaturated acids or esters can be explained by the energetics of light absorbtion and bond strengths. Figures 1A and 1B

represent the transitions and relative energies of various excited species for saturated and unsaturated acids, 27 and 28, respectively.

Scheme 5



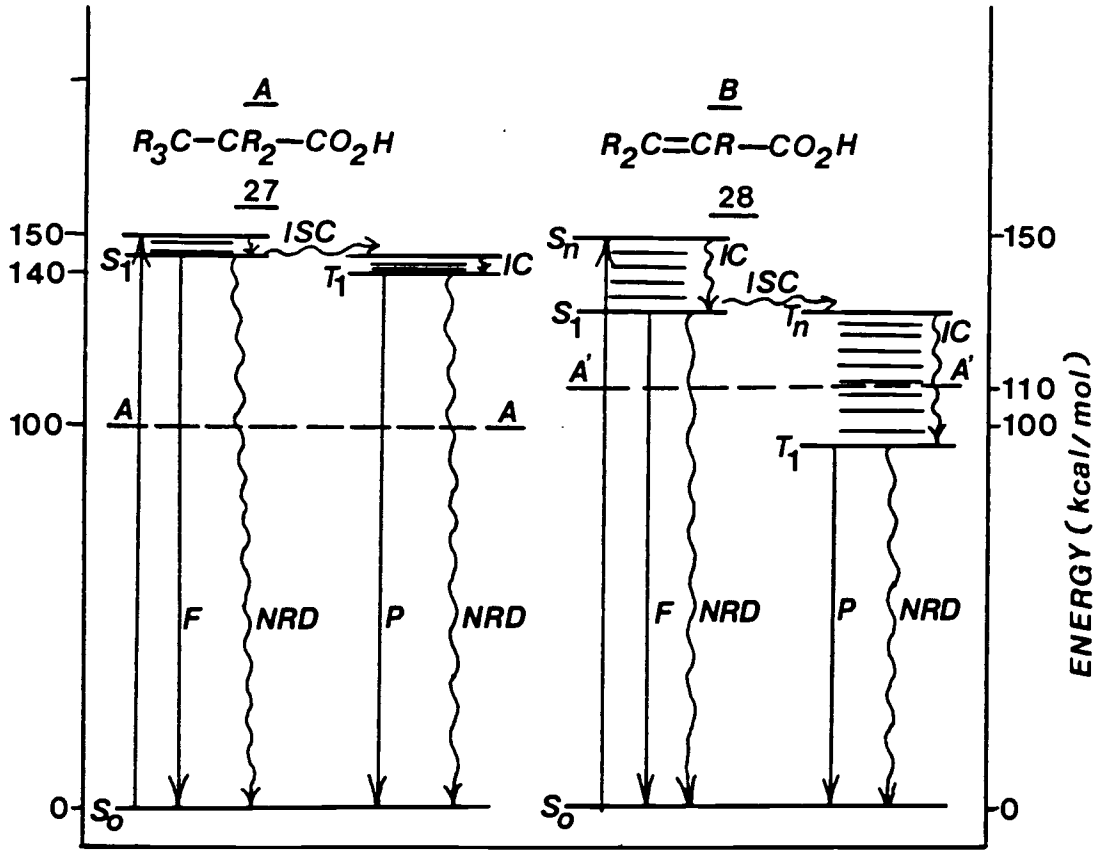
Let us examine figure 1 (side A), the saturated acid 27, in some detail and then compare this with the unsaturated acid 28, figure 1 (side B). When a highly energetic photon, 190 nm (150 kcal/mole), is absorbed by acid 27, an electron is promoted and an upper singlet excited state (π --> π^*), S_n, is generated, which undergoes rapid internal conversion (IC) to the lowest singlet excited state, S_1, by transfer of excess energy to solvent molecules. Energy loss back to the ground state, S_0, by either radiative (flourescence, F) or nonradiative decay (vibrational relaxation, NRD) lead to no chemical reaction in the molecule and thus are not important processes in the context of the current discussion. The S_1 state can undergo intersystem crossing (ISC) to an excited triplet, T_n, which again undergoes rapid internal conversion to the lowest triplet state, T_1. The energy of the T_1 state (approximately 140 kcal/mol) is

higher in energy than the bond strength of the $R_2C---CO_2H$ bond (approximately 100 kcal/mol, maximum) so bond fission is an energetically favorable process and may be competitive with decay back to the groundstate by either phophorescence (P) or nonradiative decay (NRD). On the other hand, the α,β-unsaturated acid 28 can upon irradiation go through the same sequence of promotion to S_n, IC to the lowest singlet S_1, ISC and IC to the lowest triplet, T_1. The differences between 27 and 28 are the relative values for the energy of T_1 for 28 (approximately 95 kcal/mol) and the $=CR--CO_2H$ bond strength (greater than ~110 kcal/mol due to greater sp^2 character of the bond and resonance). Thus for 28 the reactive excited state, T_1, does not have sufficient energy to cleave the bond to the carboxyl group, all the excess energy of the initial photon (150 kcal/mol) having been dissipated in nonradiative processes.

Jorgenson et al in a series of three papers on α,β-unsaturated esters with simple alkyl substituents on the β and γ positions discovered that they undergo additional photoprocesses beside simple E/Z isomerization, Scheme 6.[7,8,9] Irradiation of 29 results in a rapid photoequilibration of 29 and 30 followed by a slower formation of deconjugation product, 31, and cyclopropane derivative 32. The points to note are: irradiation in methanol-OD results in the incorporation of a deuterium at the α position in both 31 and 32, indicating that enol intermediates, 29a and 30a, are involved in the mechanism; if triplet sensitizers are present (e.g. acetophenone) no formation of 31 or 32 is detected, indicating they are formed by singlet processes; there is an induction period for the formation of 32, which rules out any common intermediate. A mechanism to account for these results is shown in Scheme 7. Abstraction of a γ hydrogen by oxygen leads to deconjugation product, 31 , whereas, abstraction of the δ hydrogen in 34 results in the formation of cyclopropane product, 32. Jorgenson also noted that there appeared to be a large solvent effect on the yield of 31. This was subsequently shown by Weedon to be a result of base impurities in the solvent .[14]

Barltrop and Wills noted parallel behavior for ethyl crotonate,

Figure 1. Energy Decay Pathways in α,β-Unsaturated Acids and Saturated Acids.



IC = INTERNAL CONVERSION

ISC = INTERSYSTEM CROSSING

P = PHOSPHORESCENCE

F = FLUORESCENCE

NRD = NONRADIATIVE DECAY

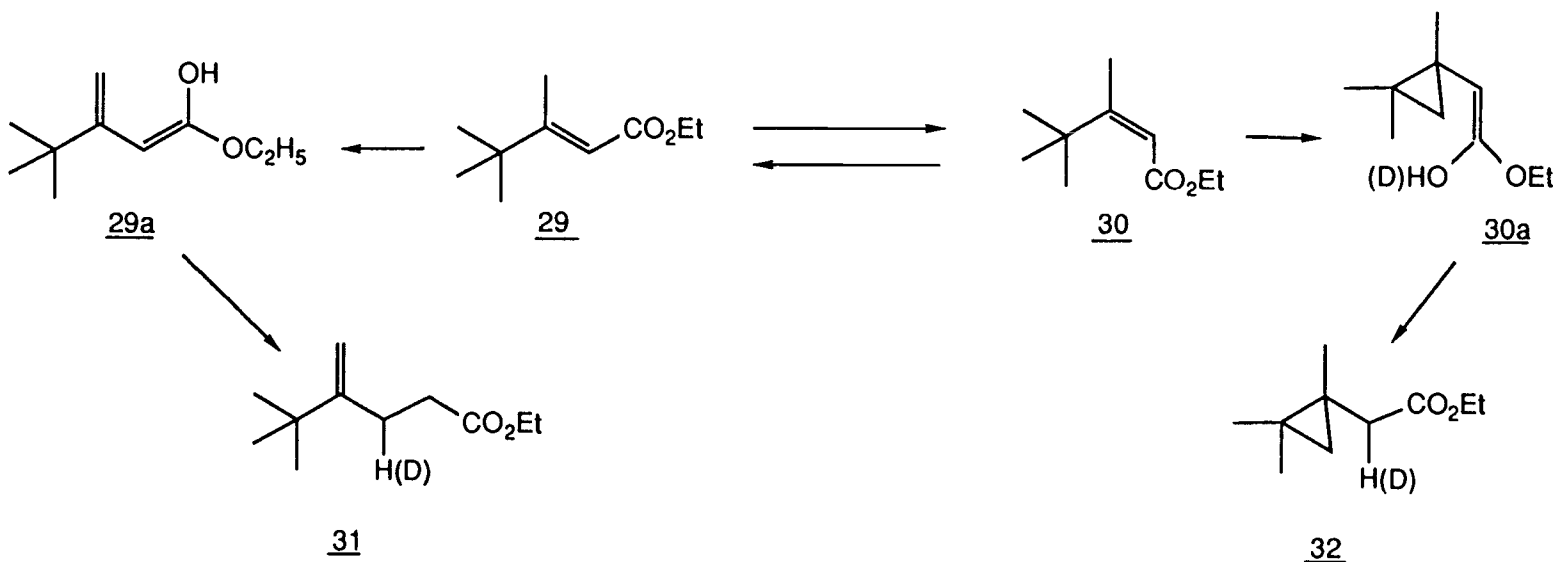
A = C-C BOND ENERGY FOR $-CR_2--COOH$

A′ = C-C BOND ENERGY FOR ==CR--COOH

= NONRADIATIVE PROCESS

= RADIATIVE PROCESS

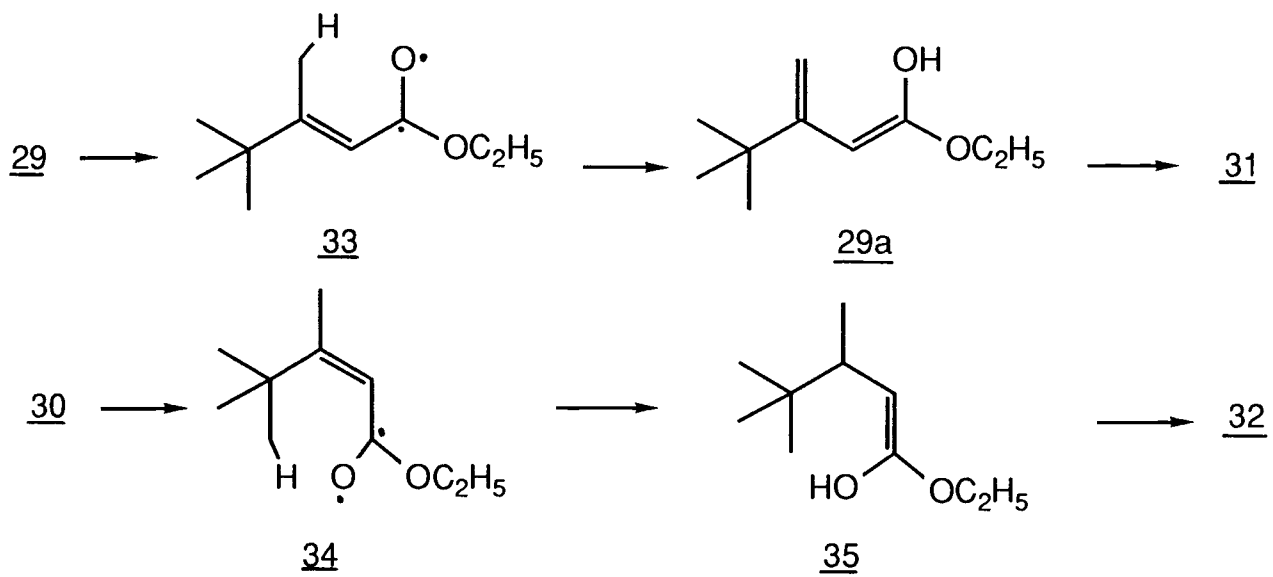
Scheme 6



29a 29 30 30a

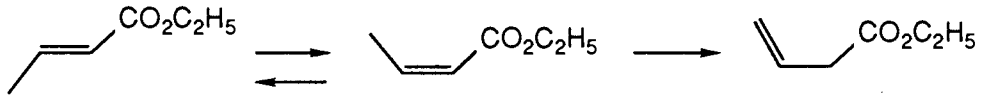
31 32

Scheme 7



Scheme 8,[10] to that of 29 (Jorgenson[7-9]). Irradiation of 25 results in photoequilibration with 26, followed by slow deconjugation, after an induction period, to 38.

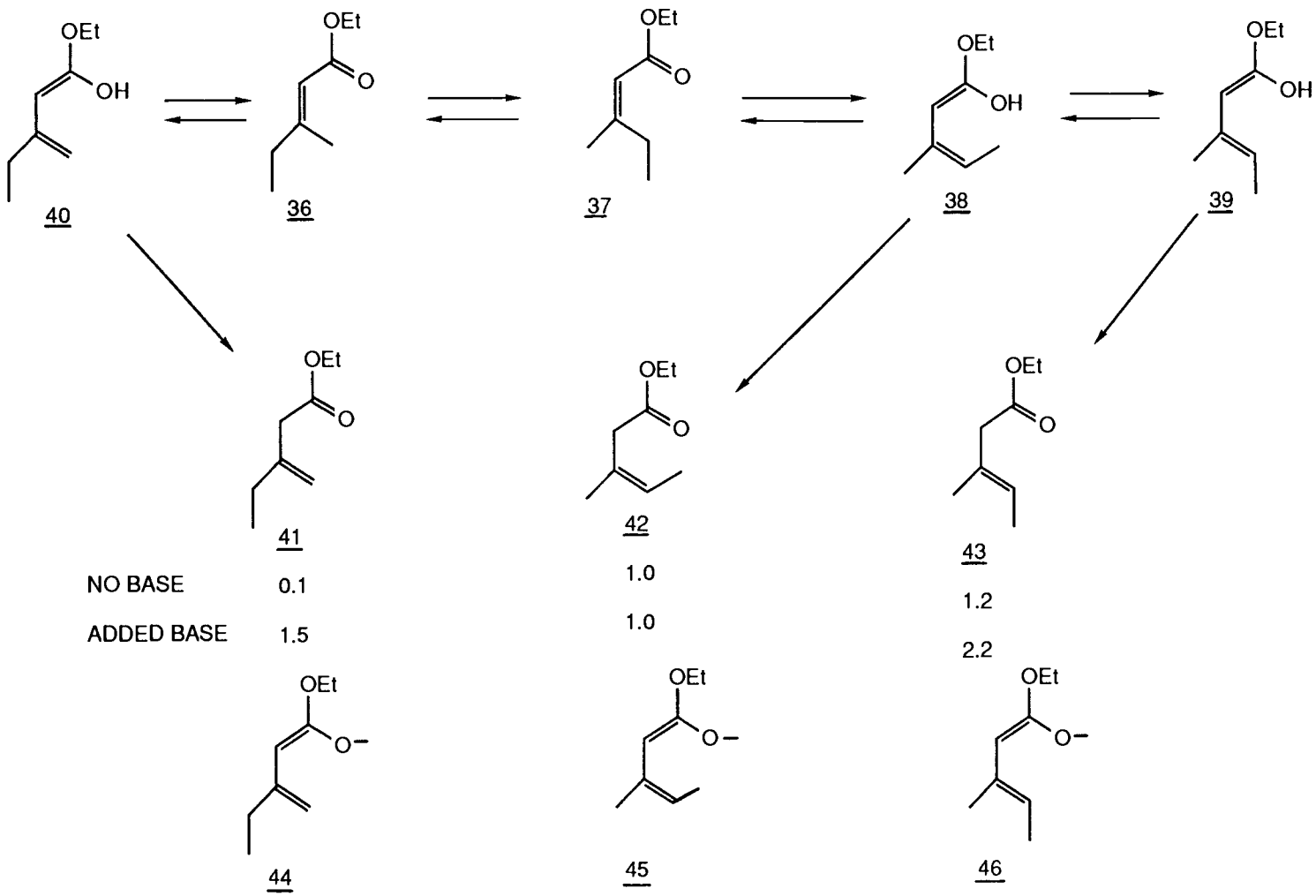
Scheme 8



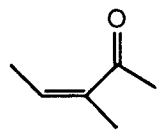
25 26 38

The photochemical deconjugation reaction of simple α,β-unsaturated esters and ketones has been studied extensively by Weedon et al.[11-15] Irradiation of ethyl (2E)-3-methyl-2-pentenoate, 36, Scheme 9, leads to a rapid E/Z isomerization of 36 and 37 by a triplet process. Photoenolization of 36 leads to photodienol 40 and photoenolization of 37 can lead to either dienol isomers 38 or 39. All three dienols have two reaction pathways available. Either a thermal [1,5,] shift of hydrogen, a suprafacially allowed process, to regenerate starting material or reketonization at the α position to form deconjugated products 41, 42 and 43. If the irradiation is carried out in the absence of base the ratio of 41:42:43 is <0.1:1:1.2. However, if the irradiation is carried out in the presence of 1,2-dimethylimidazole, a weak non-nucleophilic base, then the ratio of 41:42:43 changes dramatically to 1.5:1:2.2. The most striking feature of this result is the greatly enhanced yields of 41 and 43. Weedon goes on to suggest that this enhancement may be due to a combination of retardation of the [1,5] shift of 39 by rotation of the dienol out of the reactive s-cis configuration due to steric congestion and increased acidity of dienols 38 and 39,(due to stabilization of the conjugate bases) making deprotonation a more facile process.[15] The intermediacy of a dienolate species in the base catalysed irradiations was shown by direct observation in laser flash photoysis experiments (for more details see results and discussion section). Thus α,β-unsaturated esters which appear to be photochemically inert to deconjugation (those without γ substituents) are in fact forming the corresponding photodienol but are decaying

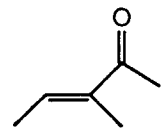
Scheme 9


OEt
OH
O
40
36
37
38
39
41
42
43
44
45
46
NO BASE
ADDED BASE
0.1
1.5
1.0
1.0
1.2
2.2
O−

back to ground state by nonradiative processes ([1,5] shift) rather than reketonizing on the α carbon to form the deconjugation product. Evidence for this nonradiative process was first observed by Morrison and Rodriquez[16] for α,β-unsaturated ketones when it was determined that the sum of the quantum yields for E/Z isomerization of 47 and 48 to a mixture of the two did not add up to unity. Since no other detectable products were formed, a non-radiative process was implicated. In the light of the work by Weedon, it seems reasonable to assume that the nonradiative process in question is photoenolization followed by thermal [1,5] shift of hydrogen to regenerate starting material.



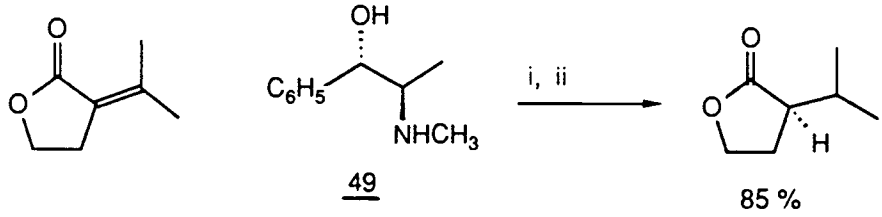
47



48

It was as long ago as 1967 that Doering and Rando suggested that the photochemical deconjugation of α,β-unsaturated esters could be a mild and convienent synthetic method.[17] Pete et al have reported the use of (-)-ephedrine, 49, to effect the enantioselective photodeconjugation of α,β-unsaturated lactones with enantiomeric excesses of up to 25%, Scheme 10.[18a-c] Although this work is in its early stages, it promises to have a good potential for synthetic applications.

Scheme 10



49

85 %

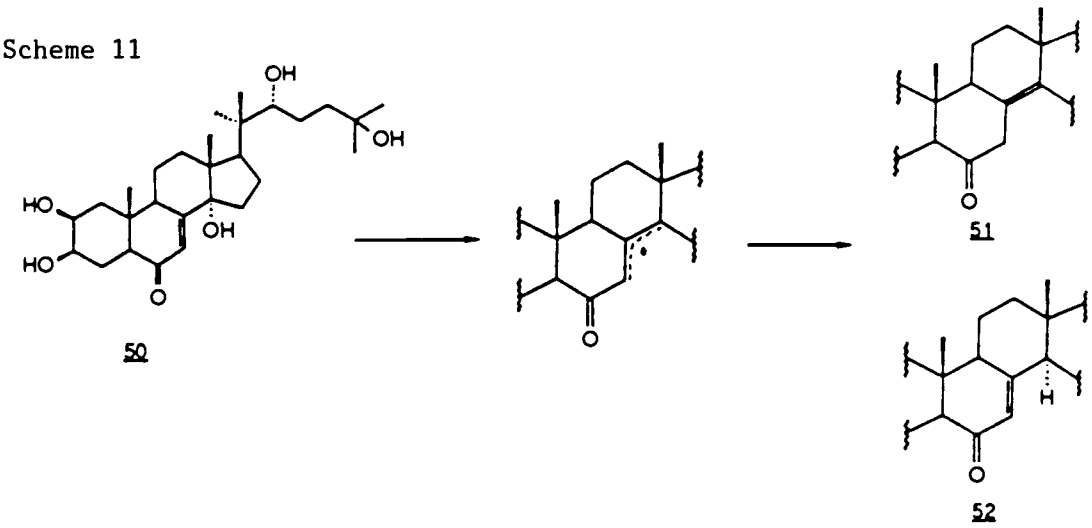
i, hv, -78°C ; ii, Pt_2O, H_2

25 % ee

20α-Hydroxyecdysone, 50, a representative insect molting hormone has been studied for its environmental photodeactivation by Danieli

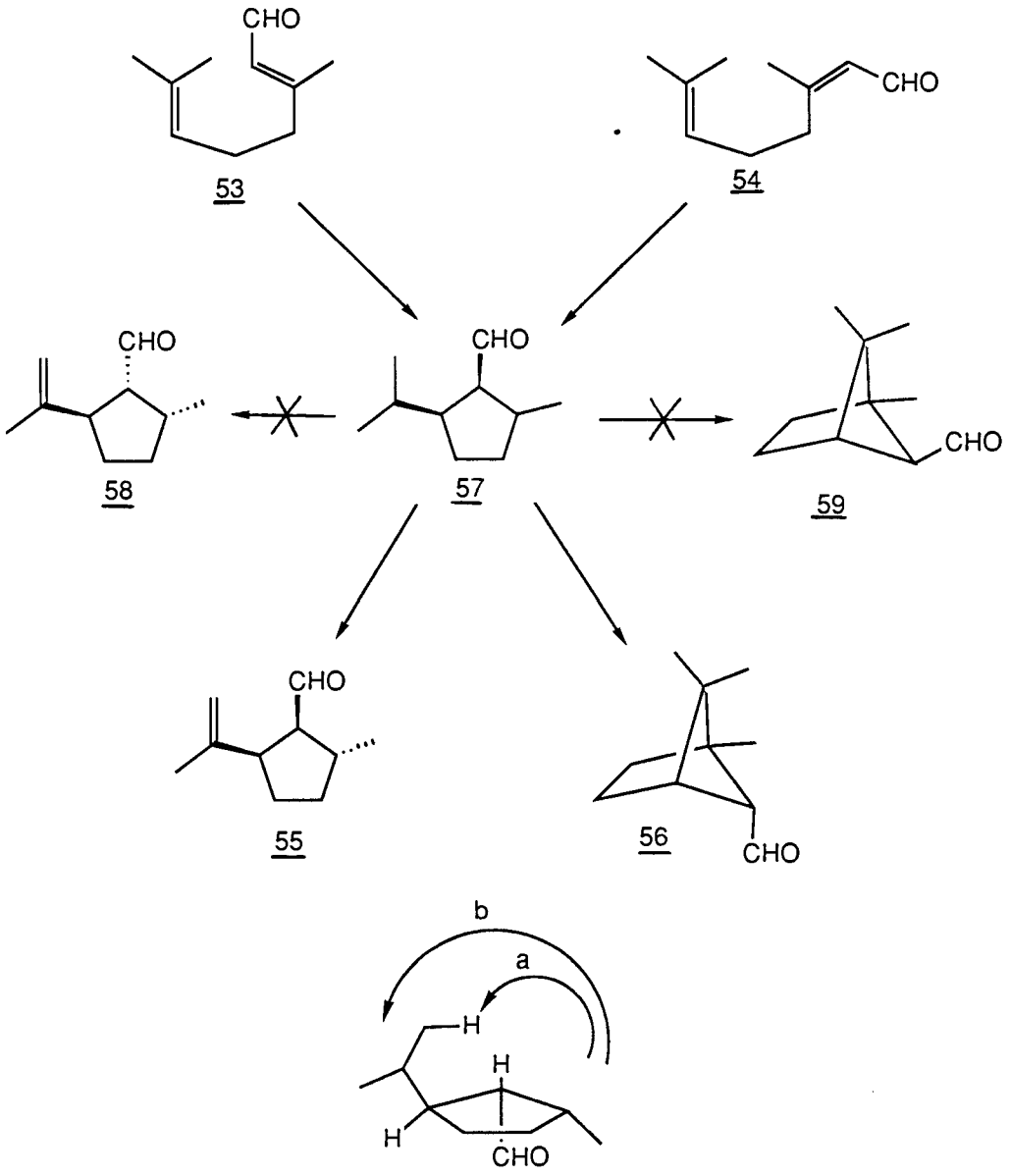
et al.[19] They report that irradiation of 50 gave a mixture of four products. The major one was found to be the deconjugation product 51 (35%), Scheme 11. Unlike the deconjugation processes discussed up to now, the authors propose a triplet intermediate (which was determined by the strong quenching of the process by oxygen ,a known triplet quencher). Excitation to the triplet followed by homolytic cleavage of the C-14 OH, leads to products 51 and 52 via hydrogen abstraction by either end of the allylic radical.

Scheme 11



Up to this point the reactions discussed have involved simple α,β-unsaturated esters, without another functional group in the molecule which could participate in the reaction. In 1962 Cookson et al reported on the photochemical transformations of citral, 53 and found that aside from the expected E/Z isomerization product, 54, two products resulting from cyclization to either a cyclopentane-carboxaldehyde derivative, 55, or a bicyclo[2.1.1]hexanecarboxaldehyde derivative, 56, Scheme 12.[20] The surprising aspect of the two cyclization reactions was the stereoselectivity of the process. The formation of 56 proceeded with the formation of only the endo isomer with no concommitant formation of the exo isomer, 59. Likewise, 55 was formed with no detectable formation of the C-1 epimer, 58. The mechanism proposed for the cyclization involved ring closure, in a crossed [2+2] photocycloaddition involving diradical intermediate 57 (closure of

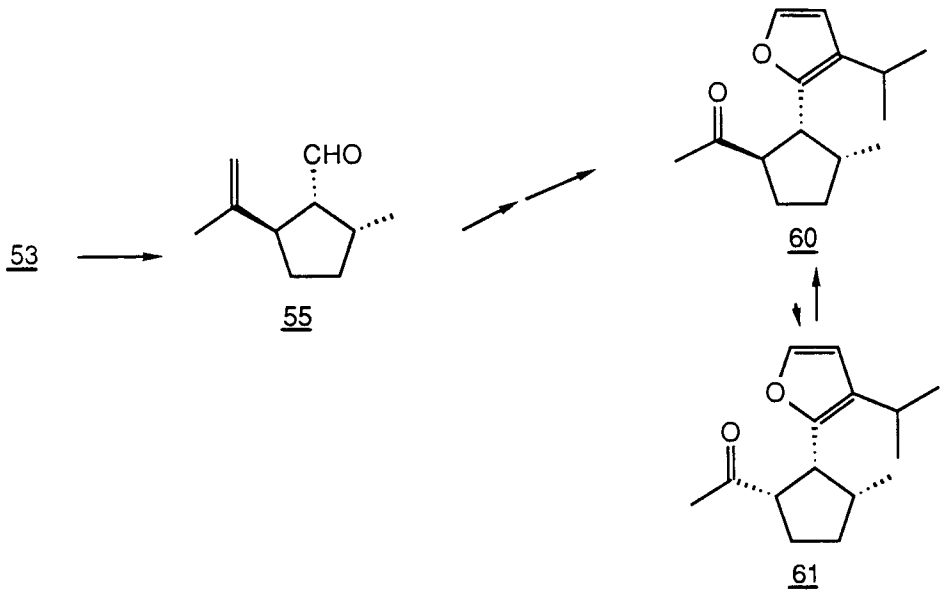
Scheme 12



1,5-hexadiene derivatives has been shown to preferentially form the bicyclo[2.1.1]hexane ring system rather than the alternate bicyclo[2.2.0]hexane ring system[21,22]. The diradical intermediate could also undergo an intramolecular disproportionation to 55, which is formed as a racemate of the diastereomer shown.

Büchi and Wüest applied this cyclization of citral to the total synthesis of (±)-furopelargones, 60 and 61 (see p.32 in the results and discussion section), Scheme 13.[47]

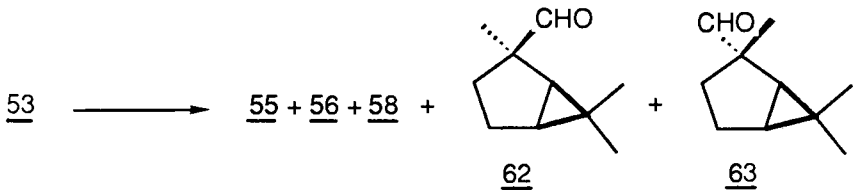
Scheme 13



An interesting series of papers by Agosta et al, describing the photochemistry of citral and some analogs at elevated temperatures, was published a few years ago.[23-25] The work highlights some of the basic differences in reactivity between α,β-unsaturated aldehydes and α,β-unsaturated esters. Irradiation of citral, 53, in various substituted benzenes (chosen for boiling points) at reflux yielded a mixture of five products, 55, 56, 58, 62 and 63, Scheme 14. At temperatures higher than 80 °C , in addition to 55, 56 and 58, two

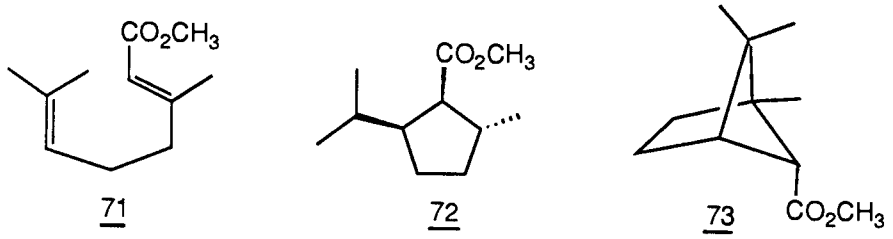
novel products of formyl group migration, 62 and 63, are formed in increasing amounts as the reaction temperature is increased. A proposed mechanism for this rearrangement involves a 1,2 migration of the formyl group via a bridged species with the unpaired electron on the oxygen, 64 or 65, Scheme 15.

Scheme 14



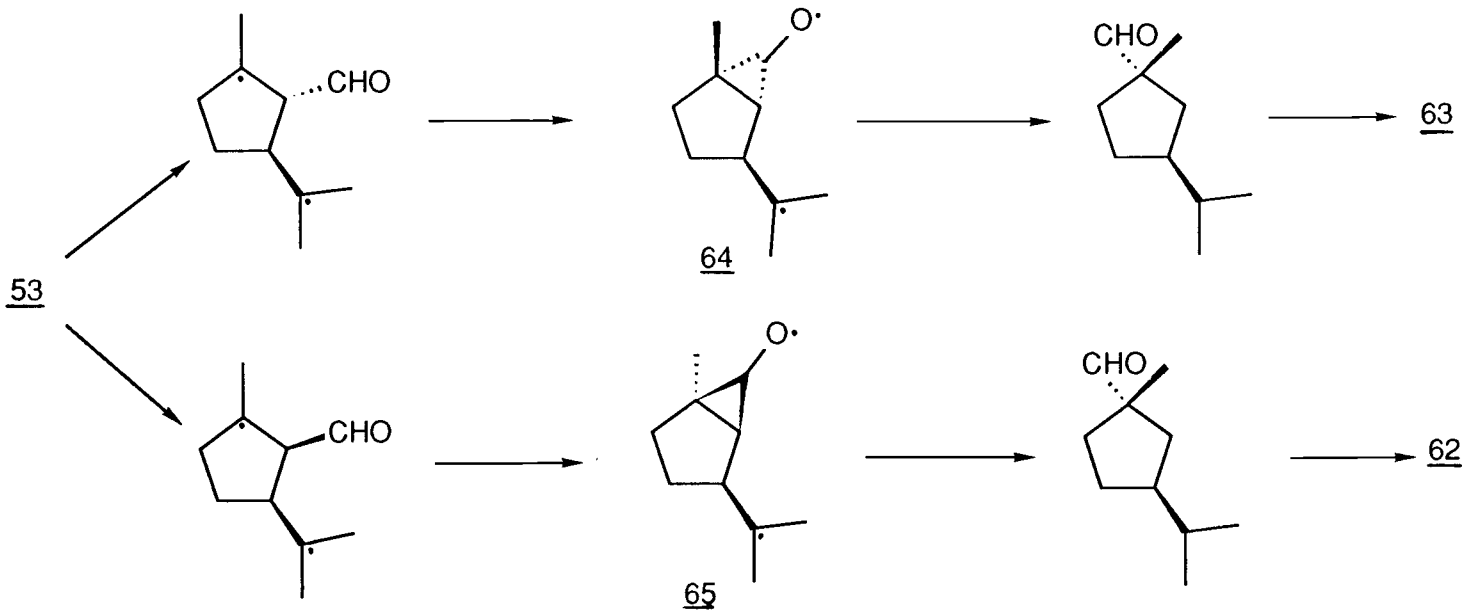
Irradiation of geranyl nitrile, 66, Scheme 16, at 130 °C generates, in addition to the two 1,6,6-trimethyl-5-cyanobicyclo-[2.1.1]hexanes, 68a and 68b, the 1,3 migration product, 67. The different behavior to migration, relative to formyl, has been explained by the added strain of the double bond to nitrogen if migration went via intermediate 70.

Irradiation of methyl geranate, 71, at elevated temperatures results only in the formation of the products expected at room temperature, 72 and 73, along with significant decomposition of starting material. Agosta made no attempt to explain this vastly different behavior of esters to aldehydes or nitriles.

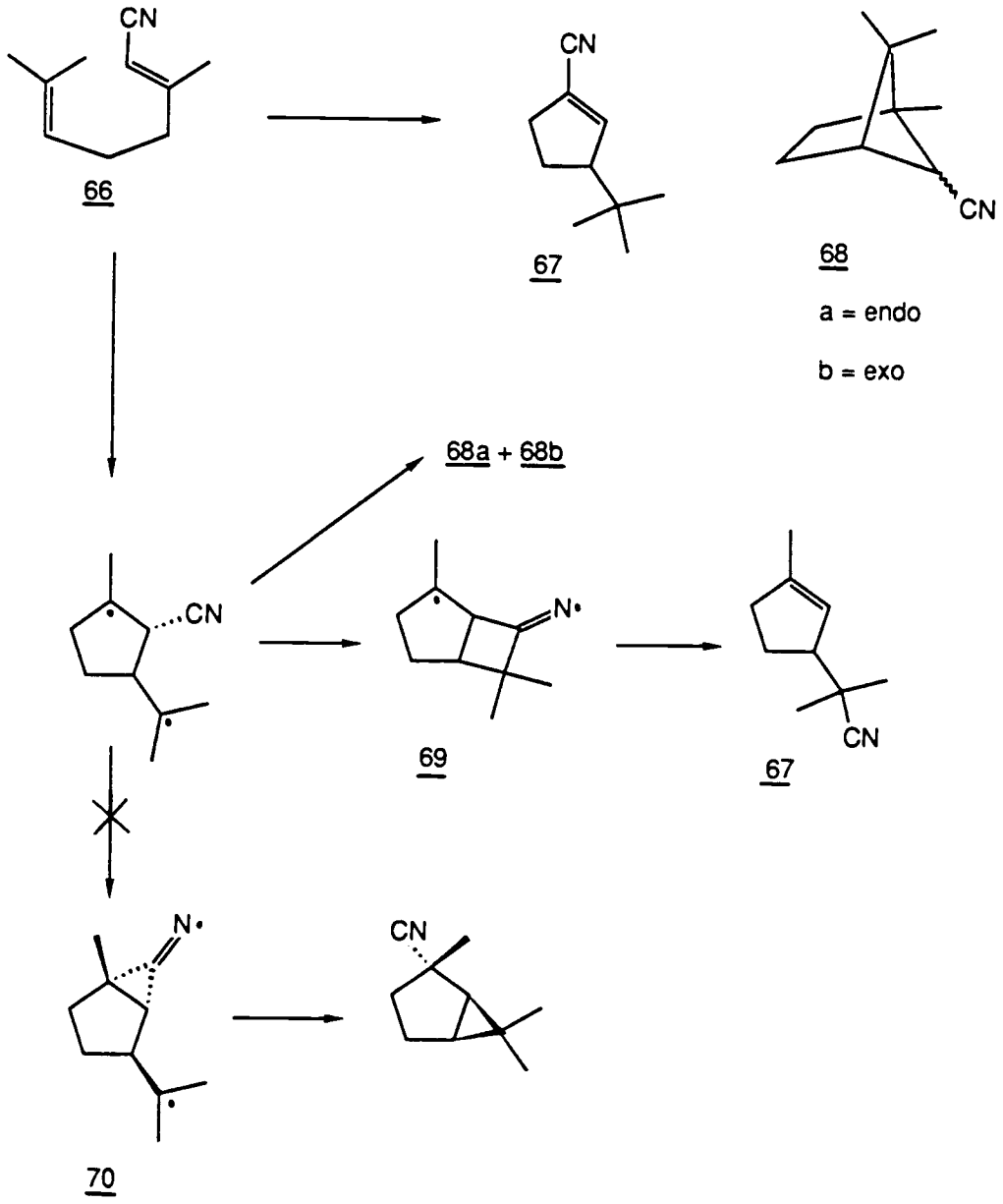


With the foundation laid for the photochemistry of α,β-unsaturated esters discussed above, we hoped to tackle the problem of

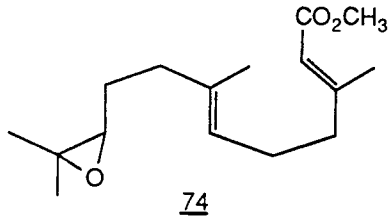
Scheme 15



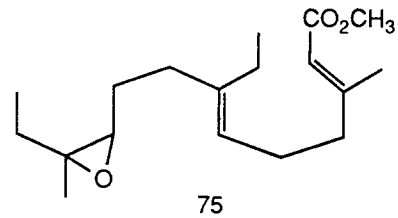
Scheme 16



phototransformations of some members of the environmentally important class of compounds known as insect growth regulators (IGR's). The IGR's are analogs of insect juvenile hormones, (74 and 75 are two examples), which are very general hormones in the insect world regulating the growth and development functions in insects. By way of an introduction to the mode of action in the control of insects by IGR's, a very brief history of the development of IGR's as insect control agents structure/reactivity considerations, and some examples of the diversity of the analogs synthesized and tested to date will be discussed.[26]



74



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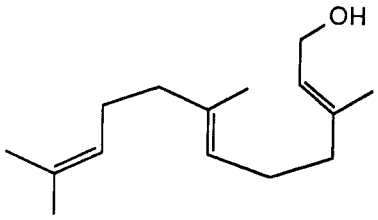
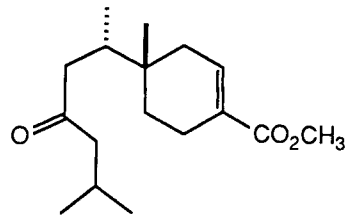
Insect juvenile hormones (IJH's) (used interchangeably with IGR's since the IJH's are the parent compounds in the series) are part of a complex interplay of three hormones which regulate an insect's growth and development. Timely hormonal release in an insect regulates development processes, such as metamorphosis from the larval to adult stage, and synchronization with changing environmental factors, such as temperature, humidity, photoperiod and food supply. Application of juvenile hormones or juvenile hormone analogs can retard or interrupt the development process, metamorphosis or hatching of eggs. The mode of action is not one of having an immediate toxic effect on the insect, but rather to inhibit development and reproduction, thereby eliminating the next generation of insect offspring.

Farnesol, 76, was the first pure compound, isolated by Schmialek in 1955, which exhibited IGR properties.[27] This discovery lead to vigorous research in the field of terpenoid compounds. Then in 1966 Slama and Williams reported that larvae, which were transported from Czechoslovakia in paper containers made with American paper, showed severe retardation of their normal growth and development cycle, while

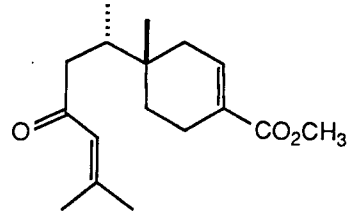
those transported in containers made of European paper showed no such effect.[28] Bowers et al isolated the "American paper factor" and determined it to be Juvabione, 77, a naturally occurring constituent of Canadian Balsam pine.[29] It was also noted that dehydrojuvabione, 78, had a higher activity as an IGR than 77. With the discovery that even minute amounts of IJH analogs can arrest or retard insect development, Williams and others put forth the idea of IGR as viable alternatives to more conventional chemical pesticides as a way of controling harmful insect pests.[30]



76



77



78

There are many advantages to the use of IGR's as insect control agents, and there are also some questions that must be answered before any specific IJH analog can reach commercial viability. Some of these points are listed below.

A. IGR's are specific to insects, but are they specific enough not to damage insects which are helpful (honey bees for instance)?

B. The IJH's are not known to have any effect on higher animals, but are the synthetic analogs similar in physiological properties?

C. the activity of IGR's is high enough that very low doses per acre can be used. For example, methoprene, 80 (figure 2), can be used to control mosquitos at a dosage of 0.0001 ppm in water.

D.It was originally thought that insects could not develop a tolerance to the application of IGR's as they have shown to be able to do in the case of traditional chemical pesticides, although this has not been shown conclusively.

E. The stability of the IGR's in the field to environmental deactivation by photochemical, hydrolytic, and biological processes, must be slow enough to have the desired effect on the insects prior to

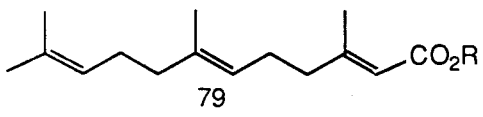
such deactivation.

F. What are the products of environmental deactivation? If the decomposition products are more toxic, or toxic and persistent, then the use of the particular IGR would not be advisable.

Since 1966 hundreds of IJH analogs have been synthesized and tested for their activity as insect growth regulators. The appendix of reference 26 gives over 340 analogs along with information about their biological activity; some of these are shown in Figure 2, 79-86, to give the reader an idea of the diversity of structural variations employed. A detailed analysis of the structure/reactivity relationships of these analogs is not possible, but some general trends can be found. The optimum molecular size seems to be based on 15 carbon sesquiterpenes (3 isoprene units) and unsaturation at C-2 in the form of an α,β-unsaturated ester has higher biological activity than the saturated counterpart. Additional unsaturation at C-6 or C-10 is less critical to the overall activity. The stereochemistry of the double bonds has a very large effect on the biological activity, with the E isomers being quite a bit more active than the Z isomers. This E vs Z isomer effect is most pronounced for the conjugated double bond at C-2,C-3. Replacement of a double bond at C-10,C-11 with an oxygen function (particularly a C-10,C-11 epoxide) increases the biological activity significantly. Epoxidation of a C-6,C-7 double bond does not have a significant effect on the biological activity. Examination of the parent compounds 74 and 75 reveals that all the factors required for high activity are incorporated into these structures.

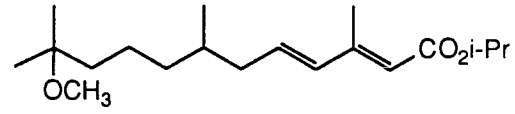
The environmental chemistry of the insect growth regulator isopropyl (2E,4E)-11-methoxy-3,7,11-trimethyl-2,4-dodecadienoate, 80,(Methoprene, Zoecon Corp., currently marketed as one of the active ingredients in "STRIKE" flea spray), has been extensively studied by workers at Zoecon Corp, [31-35] including some photochemical processes. [31,33] In an irradiation of a 0.5 ppm solution of 80 in water, through pyrex, the primary photoprocess of 80 was found to be a rapid E/Z isomerization of the C-2 double bond ($t_{½}$ ≈ 30 min) to a final photoequilibrium mixture of 44:56 2E:2Z (this is this same

Figure 2. Some Representative Insect Juvenile Hormone Analogs.[26]



79

R = Me, Et, i-Pr, etc.



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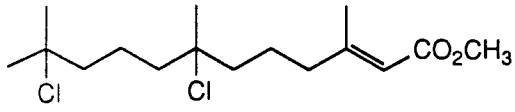
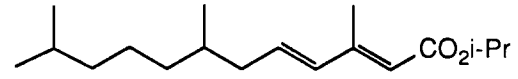


81



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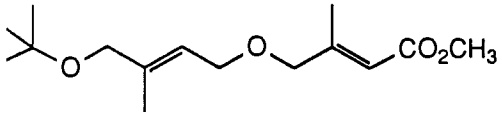
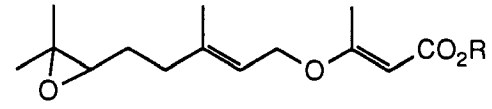
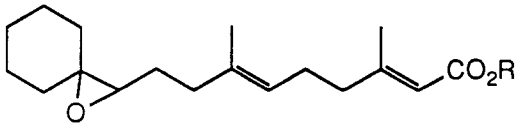


83



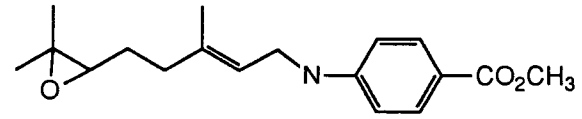
84

R = Me, Et, i-Pr, etc.

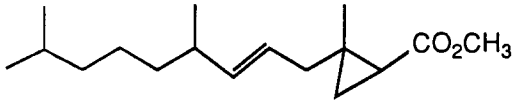


85

R = Me, Et, i-Pr, etc.



86



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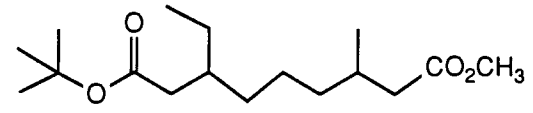
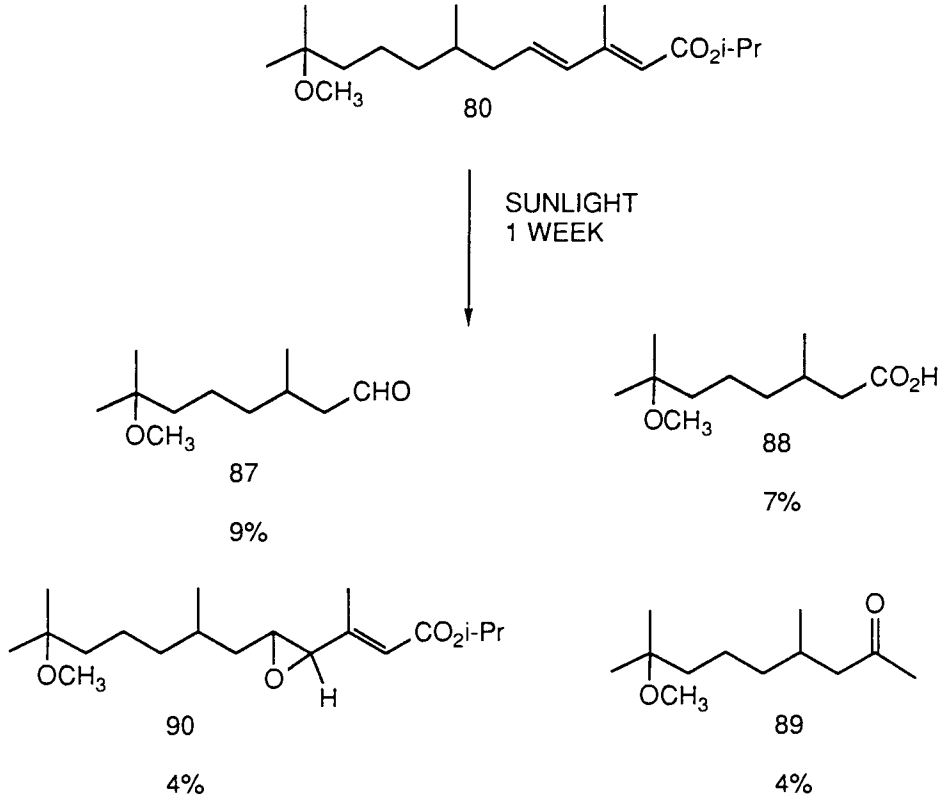


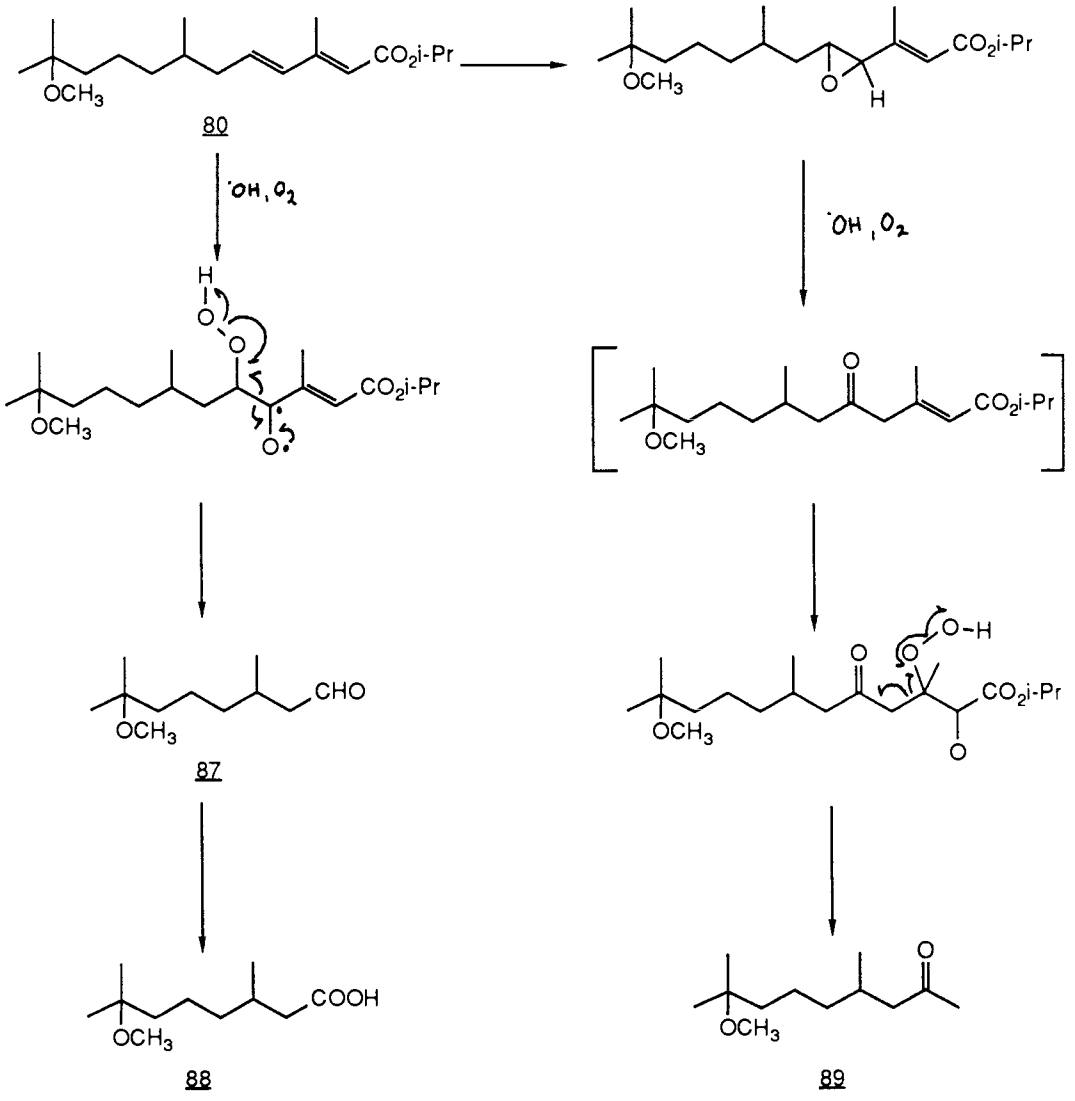
166

photostationary state that Siddall reported for hydroprene, 82[36]). The 2Z isomer was also found to have a much lower biological activity, as prior stucture/activity studies would predict, so in a relatively short time half the biological activity would be lost. Irradiation of 0.05 or 0.01 ppm solutions of 80 in water saturated with oxygen for extended periods of time (1 to 2 weeks) resulted in the complete loss of starting material ($t_{\frac{1}{2}}$ < 1 day) in conjunction with the appearance of 46 different products, Scheme 17. Only four of the products could easily be isolated and identified, 87-90. The remaining products were all formed in less than 2% each. The proposed mechanisms for the formation of 87-90 is presented in Scheme 18. The results of Siddall et al on Methoprene, 80, illustrate the rapid photochemical environmental deactivation of this IGR, and it was shown that photochemical reactions were by far the fastest deactivation processes in an extensive environmental testing program.

Scheme 17

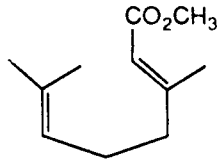

OCH3
CO2i-Pr
80
SUNLIGHT
1 WEEK
CHO
OCH3
87
9%
CO2H
OCH3
88
7%
OCH3
O
H
CO2i-Pr
90
4%
O
OCH3
89
4%

Scheme 18

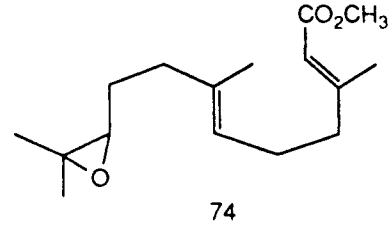

CO2i-Pr
OCH3
80
·OH, O2
H
O
O
CO2i-Pr
OCH3
O
H
·OH, O2
CO2i-Pr
OCH3
CHO
OCH3
87
O-H
O
O
CO2i-Pr
OCH3
O
COOH
OCH3
88
O
OCH3
89

RESULTS AND DISCUSSION

Before tackling the photochemistry of the insect juvenile hormone, 74d, it was felt necessary to develop a mechanistic background in the photochemistry of some simpler analogs of 74d. It was believed that the epoxide in 74d would not participate in the photochemistry since it has no significant absorption in the UV above 190 nm. It was also felt that using a symmetrically terminated molecule in the early studies would simplify the separation of photolysis products by elimination of E/Z isomers at the isolated double bond. Methyl geranate, 71, fulfilled these requirements very well. When compared to 74d it is immediately obvious that the reactive chromophores are in the correct locations as well as having the correct substitution pattern for the two double bonds.



71



74

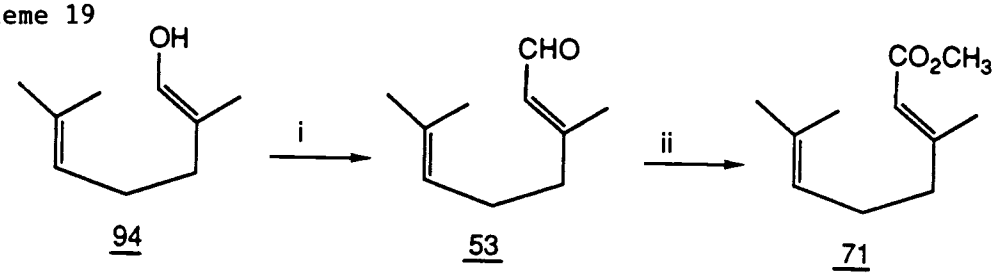
After initial irradiation experiments on the insect juvenile hormone, 74d, yielded unusual results, regarding isomerization of the isolated double bond, it was deemed necessary to look at the interaction of the α,β-unsaturated ester function with the double bond at C-6 and to establish the presence of any charge transfer character in the photochemical transformation. To do this the unsymmetrically terminated methyl (2E,6E)-3,7-dimethyl-2,6-nonadienoate, 92, and methyl (2E)-3,7-dimethyl-2-octenoate, 93b, were synthesized and irradiated under various conditions of concentration and differing solvent polarity.

The last part consisted of some preliminary irradiations of 74d to determine how general the mechanistic details developed in the model systems are when compared to an actual juvenile hormone.

Each of the model compounds listed above will be discussed in turn. The synthesis of each and the results of the photochemical studies will be cosidered separately, followed by a discussion of the overall results and conclusions.

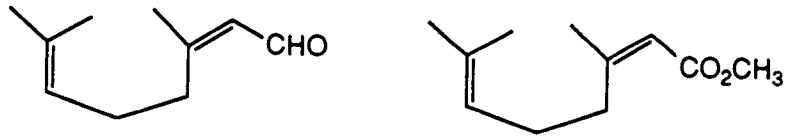
Methyl geranate, 71, was readily synthesized in two steps from geraniol, 94, Scheme 19, using the method of Corey et al.[37] Geraniol was oxidized to the aldehyde 53 (citral) with γ-MnO_2[38] in hexane (>97% yield) with no detectable isomerization to neral 96. Subsequent oxidation of the aldehyde to the methyl ester, via the cyanohydrin, with γ-MnO_2, sodium cyanide and acetic acid in methanol gave good yields (up to 70% after chromatography) of 71 with < 2% isomerization to 97. This method is applicable to a multigram scale with no loss of stereocontrol or lowering of yields.

Scheme 19



94 53 71

i. MnO_2, HEXANE, 0°C; ii. MnO_2, MeOH, NaCN, HOAc, 25°C

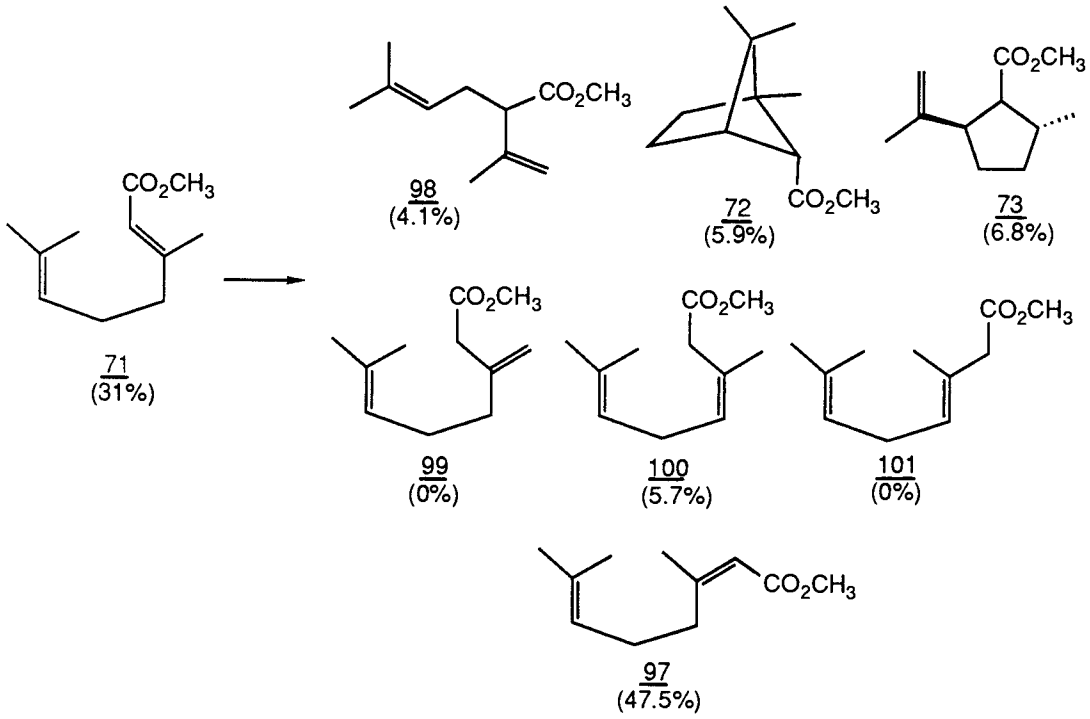


96 97

Irradiation of a 0.1 M solution of methyl geranate, 71, at 254 nm for 18.5 h lead to the formation of five product components as determined by glc analysis of the photolysis mixture, together with recovered starting material, Scheme 20. The material balance was found to be 98% (summation of peak areas before and after photolysis). Each component was collected by preparative glc and

identified by spectroscopic and chemical means.

Scheme 20



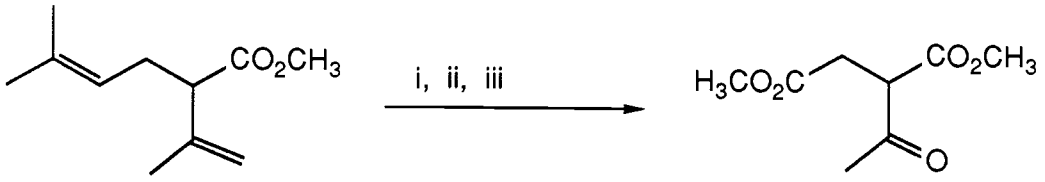
A GC-MS spectrum of each component was obtained and it was found that all the photolysis products (those present in >1.5%) were isomers of the starting material, methyl geranate, 71, as concluded from the presence of M^+ peaks at m/e 182 for each component.

The first compound to elute from the gas chromatograph was found to be methyl 5-methyl-2-isopropenyl-4-hexenoate, 98, (4.2% of the photolysis mixture). The ^1H NMR (400 MHz) spectrum reveals several structural clues. In 98 there are three vinylic protons (4.86, 4.87 and 4.99 ppm) and the expected diastereotopic nature of the two protons attached to C-3 shows as two 1H multiplets centered at 2.24 and 2.48 ppm; finally, the methine proton on C-2 at 3.01 ppm displays the expected triplet multipicity. The ^{13}C NMR (100 MHz) spectrum reveals that the carbonyl carbon has shifted downfield from 166.94 to 173.95 ppm (loss of conjugation) yet there are still four vinylic carbons, two of which (113.64 and 142.39 ppm) have the

chemical shift differences characteristic of an exo-methylene unit. Turning to the IR spectrum the most notable feature is the shift of the carbonyl stretch from 1720 cm^{-1} in methyl geranate to 1730 cm^{-1} in this compound, again indicating loss of conjugation. In the mass spectrum the fragment at m/e 69 is still the base peak, which arises from the fragmentation of the doubly allylic C2-C3 bond. So even with loss of conjugation, this molecule still has a doubly allylic bond (or its equivalent) capable of loss of the isoprenyl group.

Methyl 5-methyl-2-isopropenyl-4-hexenoate, 98, was subjected to ozonolysis followed by oxidative work-up with Jones reagent and methylation of the resulting acid with diazomethane, to give 102, Scheme 21. This compound has the expected ^1H NMR spectrum, displaying a doublet of doublets for the methylene protons and a downfield shift of the methine triplet, relative to the methine in 98.

Scheme 21

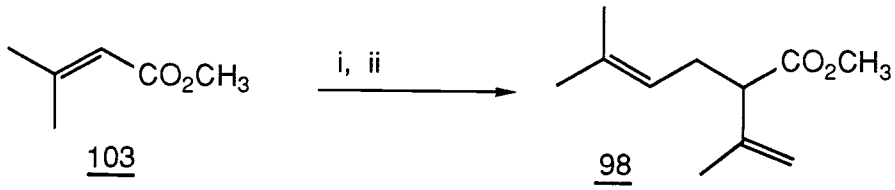


98 102

i, O_3; ii, Jones reagent; iii, CH_2N_2

As a further check on our structural assignment we found that Katzenellenbogen and Crumrine have synthesized 98,[39] Scheme 22, by alkylation of the anion of methyl senecioate, 103, with prenyl bromide. After synthesizing 98 by this methodology, we found that the spectra of the synthetic and photochemical products matched exactly. The formation of 98 can be explained as the result of a photochemical [1,3]-sigmatropic shift of the terminal isoprene unit.

Scheme 22

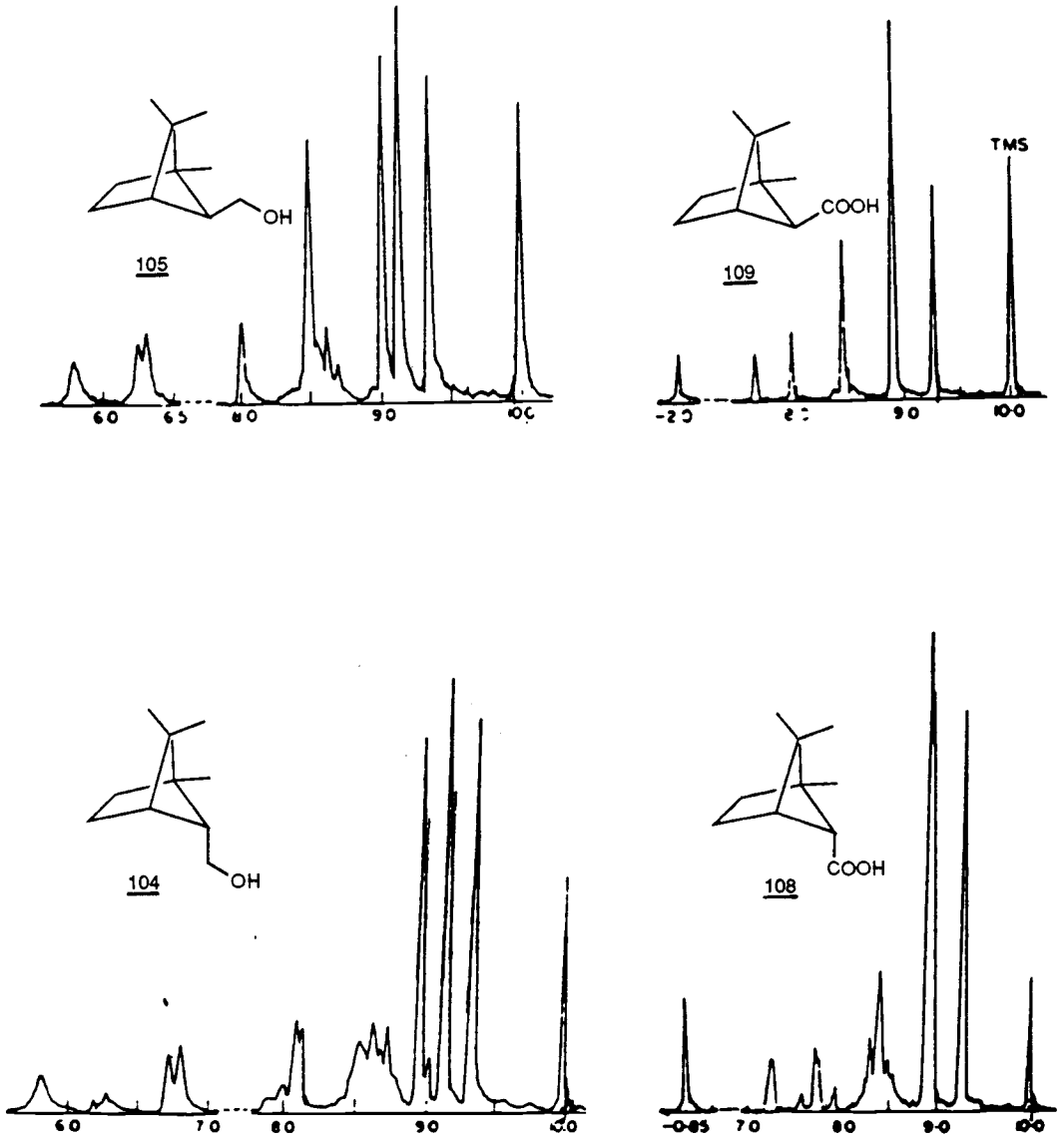


103 98

i, n-buLi, THF ii, prenyl bromide, THF

The second component to elute from the gas chromatograph was found to be 1,6,6-trimethyl-endo-5-carbomethoxybicyclo[2.1.1]hexane, 72, (5.9% of the photolysis mixture). All spectroscopic data were found to be consistent with structure 72. The proton NMR exhibited singlets for three methyl groups all attached to quaternary carbons (0.75, 1.10 and 1.11 ppm) and provided no evidence of vinylic protons. The UV spectrum consisted only of end absorption, indicating a loss of conjugation. This was confirmed by the IR stretch of the carbonyl at 1730 cm^{-1} and a downfield shift of the carbonyl carbon signal in the ^{13}C NMR from 166.94 to 173.78 ppm. However, the assignment of endo or exo to the carbomethoxy group was not done directly. This and 73 are the two compounds formed which are directly analogous to those formed in the photolysis of citral. Cookson et al, in studies on citral[20] photochemistry synthesized both endo and exo isomers for the corresponding alcohols 104, 105, aldehydes 56, 59 and acids 108, 109. Examination of the 60 MHz ^{1}H NMR spectra of these compounds, Figure 3, shows the unique nature of the endo vs exo series of compounds. The methylene signals for the endo alcohol 104 and acid 108 show a broad multiplet pattern. Whereas in the exo series, 105 and 109, these protons show a very sharp signal. The signal at 1.9 ppm, which is the bridgehead proton, in the endo series is a broad, almost flat-topped peak due to coupling with the exo proton on C-5, which forms a dihedral angle of about 30°. Conversely, in the exo series the dihedral angle between the bridgehead proton and the endo proton on C-5 is 90° and there is no coupling. Thus, the signal for the bridgehead proton is a sharp singlet in the exo series. Cooksons'

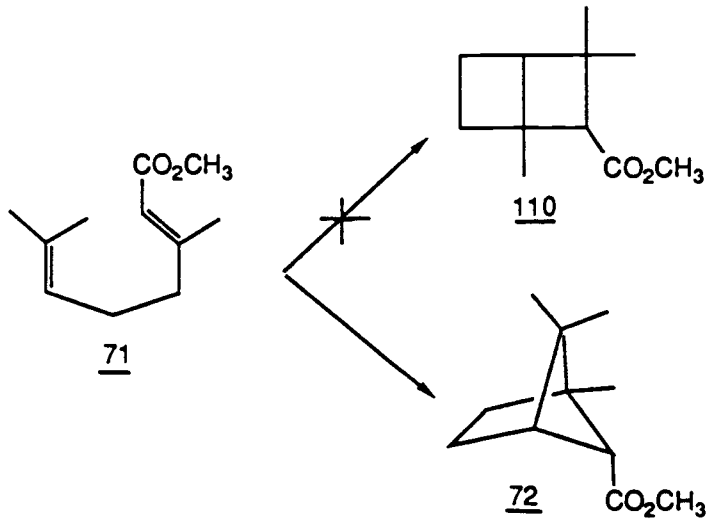
Figure 3. ^{1}H-NMR spectra (60 MHz) of Some Endo and Exo Isomers of Bicyclo[2.1.1.]hexanes.[20]



analysis of the stereochemistry was confirmed by the analysis by Meinwald on the 5-endo and 5-exo acids of the bicyclo[2.1.1]-hexanes.[40] Agosta and Wolff have studied the NMR properties of a large number of substituted bicyclo[2.1.1]hexanes, including 72, and a comparison of our spectroscopic data with that reported showed that they matched exactly.[41] In all of our studies only the 5-endo isomer was ever detected with no hint of formation of the 5-exo isomer.

Initially in the course of this research a second possible structure for 72 that had to be considered was a bicyclo[2.2.0]hexane skeleton 110. This type of skeleton was ruled out by the correlation of the photochemical product, 72, with known compounds, as well as a large body of evidence which shows that 1,5-hexadienes, both substituted and unsubstituted, undergo crossed [2+2] photocyclo-additions to form the bicyclo[2.1.1]hexane ring system rather than the bicyclo[2.2.0] hexane ring system, Scheme 23.[21,43,44]

Scheme 23



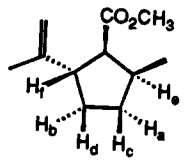
The third compound to elute from the gas chromatograph was methyl 2-isopropenyl-5-methylcyclopentanecarboxylate, 73, (6.8% of the photolysis mixture). This compound was also isomeric with starting material ,71, and showed two vinylic protons in the ^{1}H-NMR (4.70 and 4.99 ppm). Two widely spaced vinyl signals in the ^{13}C-NMR at 109.37 and 146.93 ppm, which are highly indicative of an exo methylene

group,[45,46] along with a downfield shift of the carbonyl carbon from 166.94 to 174.98 ppm indicated deconjugation. Deconjugation of the ester was also supported by the UV spectrum which showed only end absoption and by the IR spectrum with a shift of the carbonyl peak from 1720 to 1730 cm^{-1}. A two dimensional ^{1}H-^{1}H shift correlated spectrum (^{1}H-COSY45) (details are in the experimental section) was also run, Figure 4, showing that the assignments are consistent with the proposed structure. The feature to note on the ^{1}H-COSY45 spectrum is that the 2H multiplet at 1.4 ppm corresponds to the two vicinal protons on C-3 and C-4 which are trans to the carbomethoxy group and in approximately the normal location for methylene protons. The other 2H multiplet at 1.9 ppm corresponds to the other vicinal pair of protons on C-3 and C-4 which are cis to the carbomethoxy. These cis protons have been shifted downfield approximately 0.5 ppm from the normal location of a methylene proton, presumably due to the deshielding effect of the carbomethoxy group. These four protons attached to C-3 and C-4 would be expected to have different chemical shifts in any case since they are diastereotopic pairs. The question of whether the multiplets centered at 1.4 and 1.9 ppm are geminal or vicinal pairs of protons is unambiguously answered by examination of the ^{1}H-^{13} shift correlated spectrum (HETCOR) for 73, Figure 5. This 2-D NMR technique correlates the carbon spectrum (f-2 axis, X) with the proton spectrum (f-1 axis, Y). Protons attached to a specific carbon show up as peaks on the intersection of projections through the carbon and proton of interest (clearly if a proton is not on the carbon in question there will be no peak at the intersection of the projections). If two protons of different chemical shift are attached to the same carbon (e.g. as in the methylene signals of 73) then the projection of the one carbon intersects two proton projections, i.e two peaks on the line. For 73 it can be seen that the carbon at 30.5 ppm has attached to it protons with chemical shift of 1.41 and 1.91 ppm. Likewise, the carbon at 34 ppm has attached to it protons with chemical shifts of 1.31 and 1.85 ppm. This result is consistent with the structure assignment already given. The quaternary carbon in the vinyl group is outside the

spectral window since it would not correlate with any protons in the spectrum, but would just lower the signal-to-noise ratio by having to enlarge the spectral window. The distinction of the chemical shifts is lost in the proton NMR spectrum but does manifest itself in the ^{1}H-COSY45 and HETCOR spectra. However, it is not possible to unravel information about coupling constants from either of these techniques. So in an attempt to gain information about the coupling constants, and thereby information about stereochemistry, a J-resolved spectrum (JRES) was run . This 2-D NMR technique (details are described in the experimental section) affords chemical shift along the X (f2) axis and couplings in hertz along the Y (f1) axis, Figure 6. Examination of projections parallel to the f1 axis, Figure 7, shows that all the couplings in the complex multiplets at 1.4 and 1.9 ppm resolve themselves as distinct signals at 1.31, 1.41, 1.85 and 1.91 ppm. Even though the extreme complexity and second order nature of these multiplets precludes assignment of coupling constants in this example, it does illustrate the power of this technique to unravel complex, overlapping multiplets and give the couplings (solvable or not).

The question of stereochemistry in the photocyclization reaction of citral was addressed by Büchi and Wüest.[47] It had been shown that the photocyclization of citral, 53, is a triplet process and would proceed via conformation 111 of the P-state, Scheme 24, rather than conformation 112 due to less steric crowding of the isoprenyl group by the formyl group.[37] This leads to the triplet biradical species 113 with the formyl and isopropyl trans to one another. Following intersystem crossing, this biradical has two competing reaction pathways available. Path a is an intramolecular disproportionation reaction of 113, which is favored by the intermediacy of a six membered ring in the transition state leading to the formation of 55. It is interesting to note that two of the three chiral centers are set by the initial cyclization and the third center is a direct consequence of the intramolecular nature of the disproportionation reaction. Path b is an intramolecular coupling reaction of the biradical intermediate, 113. The stereocenter at C-5 is again predetermined by the initial cyclization of intermediate 111,

Figure 4. ^{1}H-COSY45 Spectrum of Methyl 2-isopropenyl-5-methylcyclopentanecarboxylate, 73.



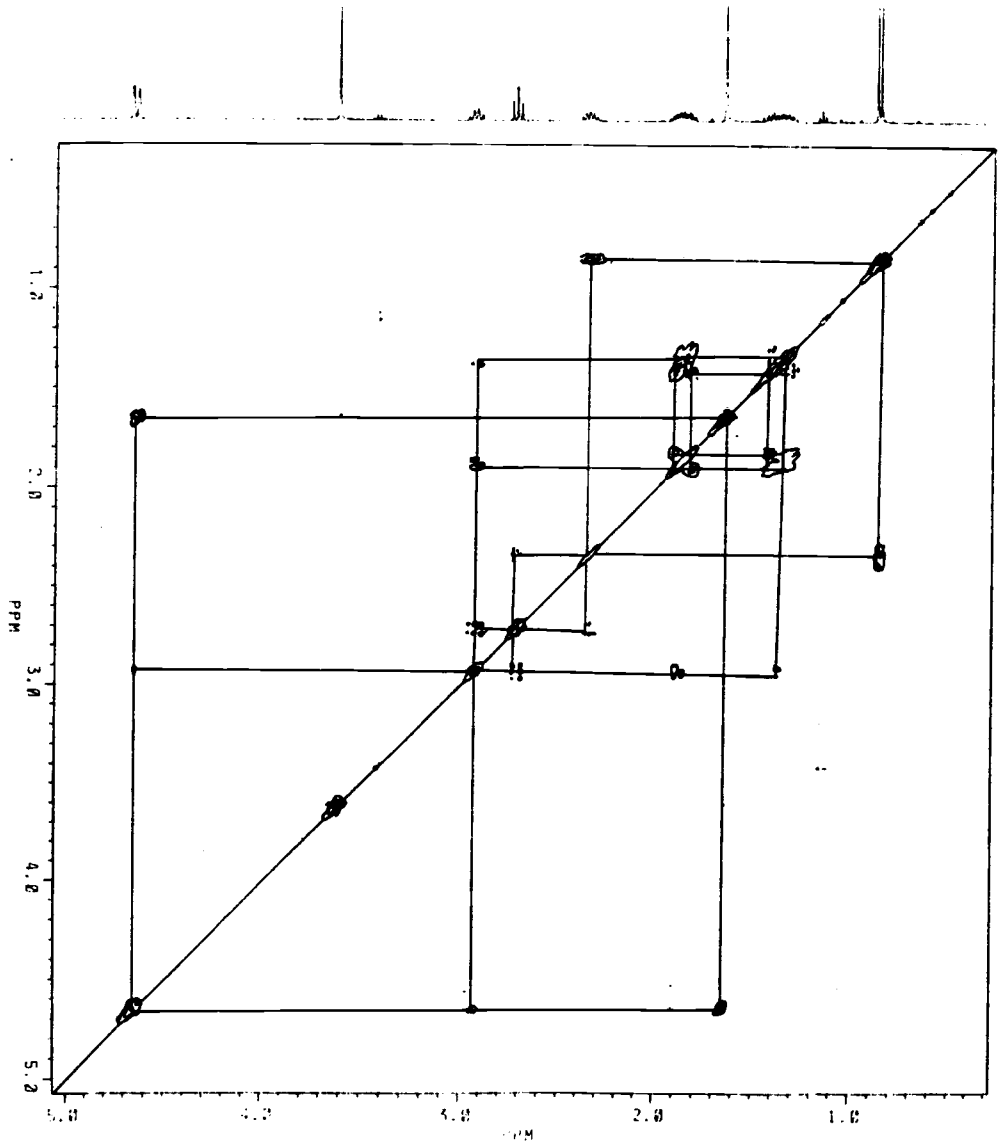


Figure 5. ^{1}H, ^{13}C HETCOR Spectrum of Methyl 2-isopropenyl-5-methyl-cyclopentanecarboxylate, 73.

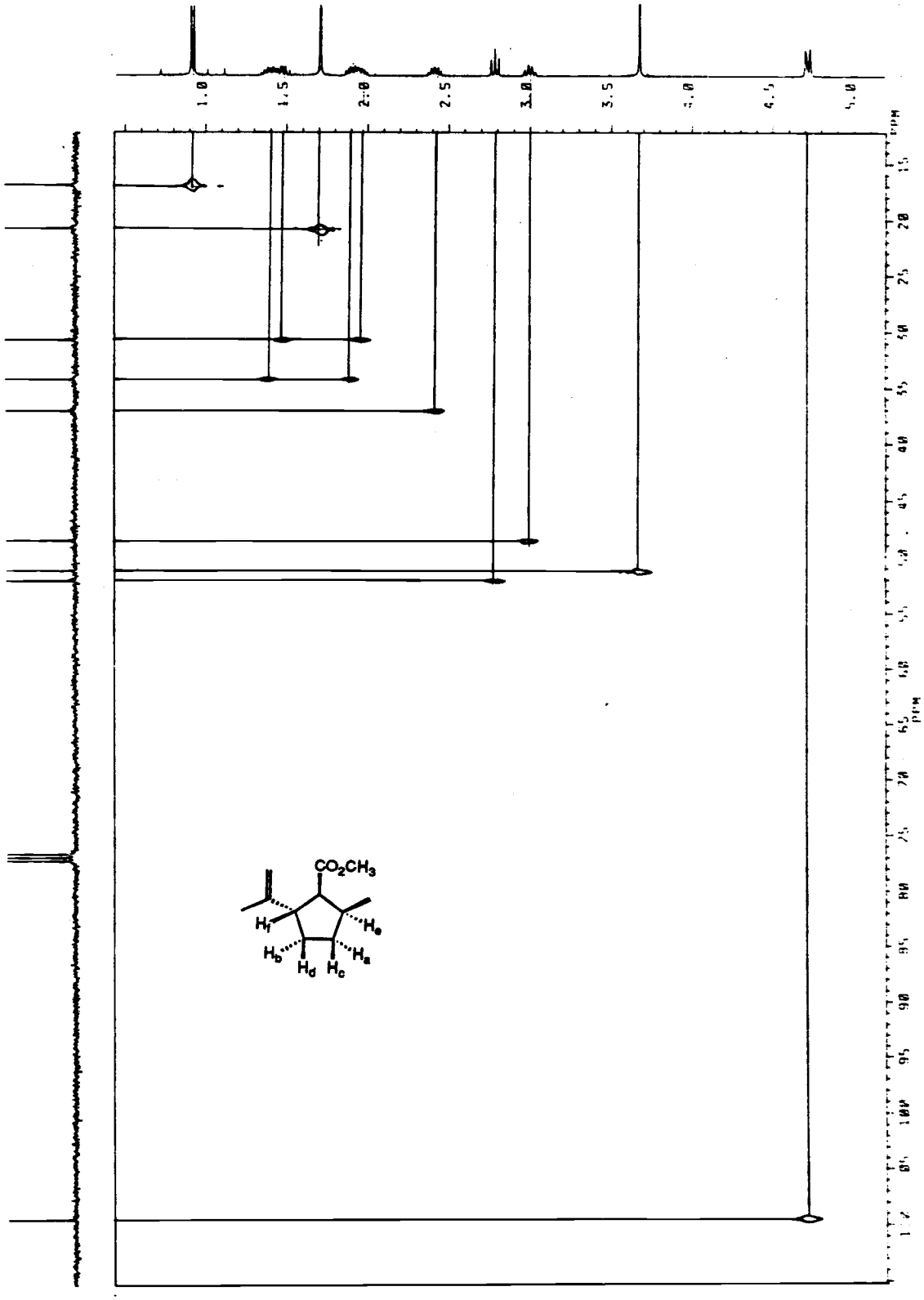


Figure 6. JRES Spectrum of Methyl 2-isopropenyl-5-methyl cyclo pentanecarboxylate, 73.

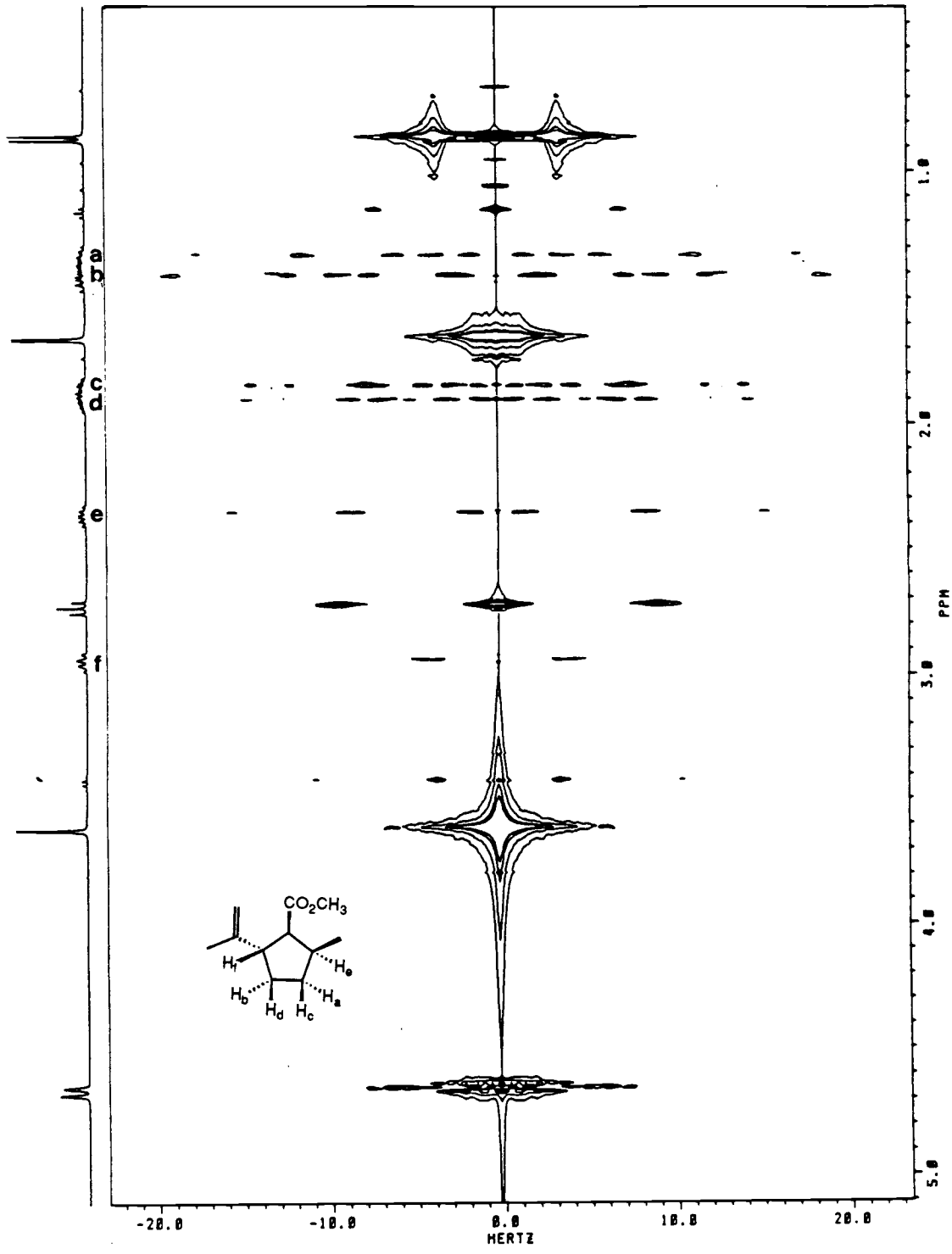
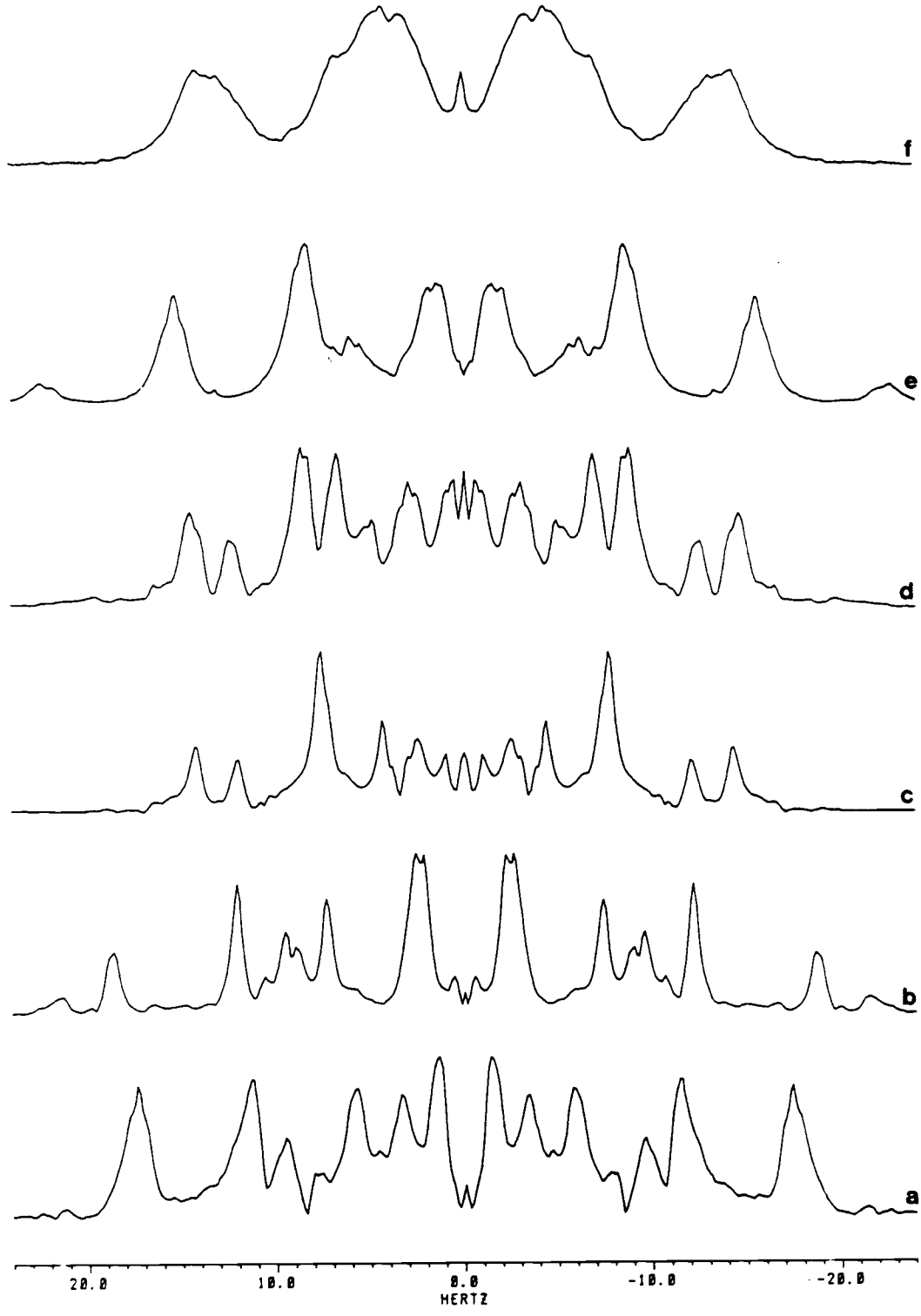
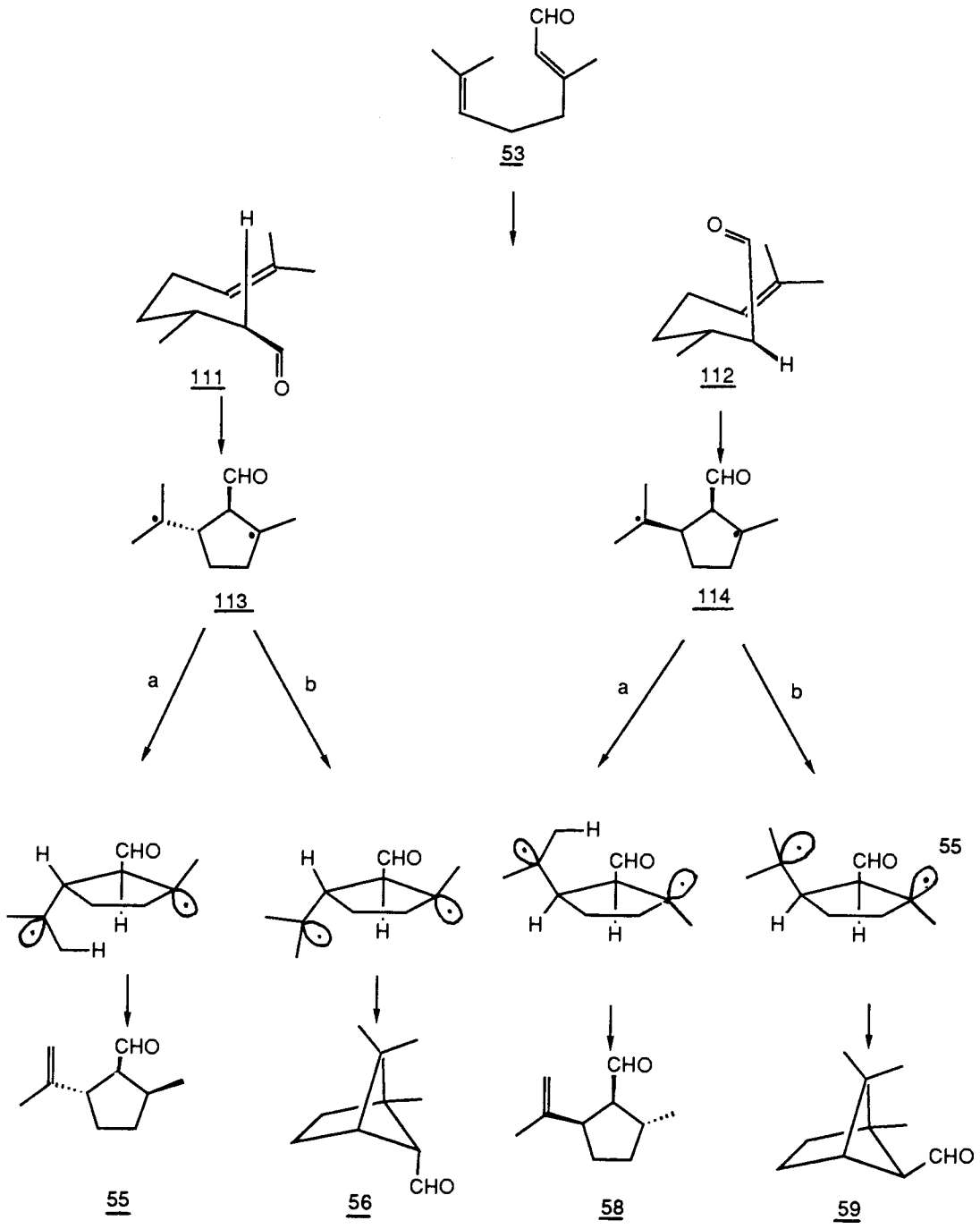


Figure 7. Projections in the f1 (Y) Axis of the JRES Spectrum of Methyl 2-isopropenyl-5-methyl cyclopentanecarboxylate, 73.



Scheme 24

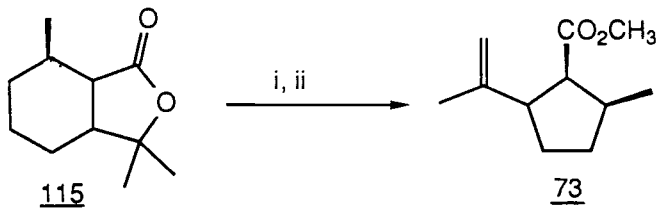

CHO
53
H
O
111
O
H
112
CHO
113
CHO
114
a
b
a
b
H
CHO
H
H
H
CHO
H
H
CHO
H
H
CHO
H
55
CHO
55
CHO
56
CHO
58
CHO
59

which leads to the endo isomer 56. Büchi found that epimerization of 55 in sodium methoxide/methanol yielded a 60:40 mixture of 55 and 58. Thus the formyl group has a slight preference to be trans from the bulky isopropenyl group. It should be kept in mind that even though a ground state epimerization with sodium methoxide leads to a 60:40 mixture of epimers, in the photocyclization only one epimer (one pair of enantiomers) is formed. In the case of photocyclization of methyl geranate, 71, the selectivity for placing the carbomethoxy group (bulkier than formyl) trans to the isopropenyl group should be even greater and only one epimer has ever been detected. Preliminary epimerization results with sodium methoxide indicate that this molecule does not epimerize. This is based on glc analysis; however, the two epimers may not separate under the glc conditions used, so a 400 MHz ^{1}H-NMR spectrum was obtained and found to be identical to the spectrum of starting material. If epimerization did indeed occur then the signals for the methine protons on C-1, C-2 and C-5 would all be expected to shift significantly.[49] The proton on C-1 would be trans to the isopropenyl group and have a completely different magnetic environment than the C-1 proton (cis to the isopropenyl) in starting material. The proton on C-2 would also exhibit a significant change in its chemical shift, moving from a position cis to the carbomethoxy to the trans position (an expected upfield shift).

The structure of 73 produced in the irradiation of 71 was shown to be identical, by comparison of spectroscopic data (IR, ^{1}H-NMR), to 73 obtained by Wolinsky and Eustace from the high temperature base catalysed ring opening of lactone 115, Scheme 25.[48,49]

The fifth component to elute from the gas chromatograph in the direct irradiation of 71 was readily identified as methyl (2Z)-3,7-dimethyl2,6-octadienoate, 97 (47.5% of the photolysis mixture). Comparison of the glc retention times as well as spectroscopic properties (^{1}H-NMR, ^{13}C-NMR, IR, UV and MS) of the photolysis product and a known sample of 97 showed the two to be identical. The authentic sample of 97 used in the comparison was synthesized from citral, which comes as a 60/40 mixture of E/Z isomers, by the method of Corey et al, as previously descibed.[37]

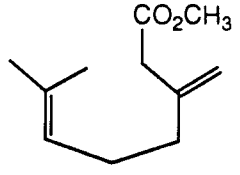
Scheme 25



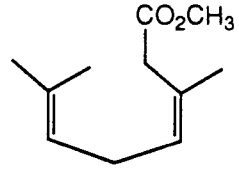
115 73

i, KOt-bu, DMF,110 C ii, CH_2N_2

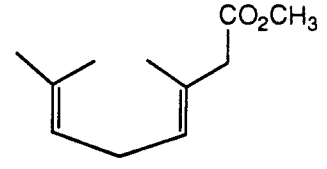
In the direct irradiation of 71 in ether, with scrupulous exclusion of base, only one photodeconjugation product could be isolated and identified: methyl (3Z)-3,7-dimethyl-3,6-octadienoate, 100. This product was formed in 5.7% and was the fourth compound to elute from the gas chromatograph. In the presence of a weak, non-nucleophilic base, 1,2-dimethylimidazole (1,2-DMI), two products are formed in addition to those already mentioned. They are both isomeric with starting material and are the other two possible deconjugation products: methyl 3-methylene-7-methyl-6-octenoate, 99, and methyl (3E)-3,7-dimethyl-3,6-octadienoate, 101. At this time these additional products, which are not formed in detectable amounts



99



100



101

in the direct irradiation, are introduced for the purpose of establishing their structures. The details of the mechanism and kinetics of their formation will be discussed at length below.

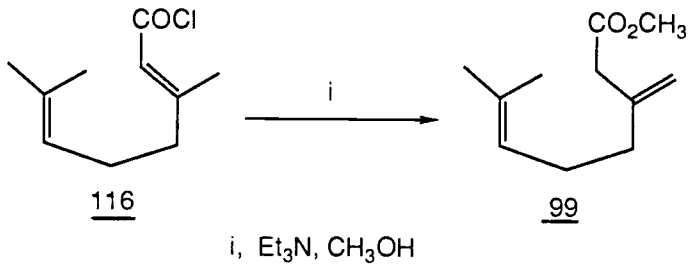
Identification of 99 was straightforward. The UV and IR spectra both showed a loss of conjugation and analysis of the mass spectrum showed that this compound is indeed an isomer of starting material, the M^+ is at m/e 182. An analysis of the ^{1}H-NMR spectrum showed that there were three vinylic protons with a downfield shift of the C-2 methylene protons to 3.07 ppm since they are both allylic as well

as alpha to the carbomethoxy group. The ^{13}C-NMR spectrum still shows four alkene carbons, two of which have the characteristic chemical shift differences of an exo-methylene group.

Wolinsky and Bedoukian have synthesized 99 by deconjugation of the geranyl chloride,[50] 116, using the method of Iwakura,[51] Scheme 26. Spectroscopic properties (IR, NMR, MS) in the literature all matched those of the product 99 from the photolysis.

The remaining two products, 100 and 101 were found to be the result of in chain deconjugation to the isomeric E (101) and Z (100) compounds and identification of these compounds was readily accomplished. All the spectra, IR, NMR (both proton and carbon), MS and UV, were surprisingly similar and could be used to assign the

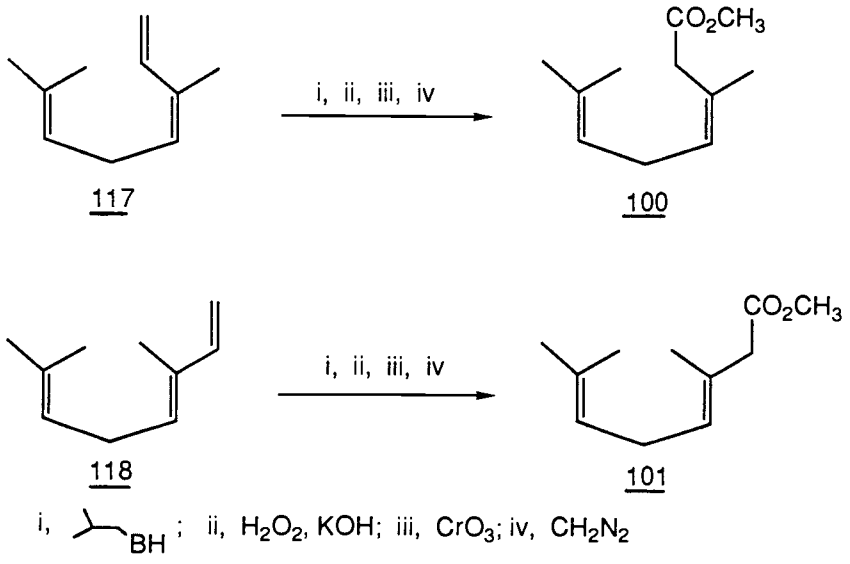
Scheme 26



basic carbon skeleton but could not on cursory examination be used to differentiate the E from Z isomer. As was stated earlier the mass spectrum shows that these compounds are isomers of the starting material 71 (M^+ is at m/e 182). UV, IR and ^{13}C NMR spectroscopic measurements all indicated loss of conjugation. The UV spectrum showed end absorption only, the IR showed that the carbonyl peak shifted from 1720 to 1730 cm^{-1} and the carbonyl carbon shifted downfield from 166 to 172 ppm in the ^{13}C NMR spectra. Analysis of the ^{1}H-NMR spectra revealed the expected features for the proposed structures. Two 1H vinylic triplets as well as a triplet for the methylene protons on C-5 (broadened by allylic coupling), three methyl singlets and the C-2 methylene singlet at 3.08 ppm which is shifted downfield due to the fact that it is both allylic and alpha to the carbomethoxy group. ^{1}H-COSY45 spectra were run on the Z and E isomer, 100 and 101

respectively, and the assignments are as shown in Figures 8 and 9. The ^{1}H-COSY spectrum for 100, Figure 8, confirms the assignments that one would make from the straight proton NMR spectrum with the one exception that the two vinyl protons are unambiguosly assigned by the COSY. Erman [52] has synthesized both the E and Z isomers of these deconjugation products: 100 from cis-ocimene, 117 and 101 from trans-ocimene, 118, Scheme 27. The reported spectroscopic properties are identical with the samples 100 and 101, with the following differences: chemical shifts for the vinyl protons are correct, but the assignment is opposite to that obtained via the ^{1}H-COSY45 spectrum and the chemical shift for the C-2 methylene protons in 100 is upfield by 0.58 ppm (this may be attributed to an error in Ermans' paper as the chemical shift for the same protons in 101 is correct). A HETCOR spectrum was also run on both isomers, Figure 10,

Scheme 27



100, and Figure 11, 101. This technique allows an unambiguous assignment of the carbon spectrum, assuming that the proton spectrum has been assigned by ^{1}H-COSY45 or other method. Examination of the two HETCOR spectra show that all the carbon lines stay essentially fixed in going from the E (101) to Z (100) isomer except for methylene carbon, C-2, which shifts upfield by 7.6 ppm, and the methyl attached

Figure 8. ^{1}H-COSY45 Spectrum of Methyl (3Z)-3,7-Dimethyl-3,6-octa dienoate, 100.

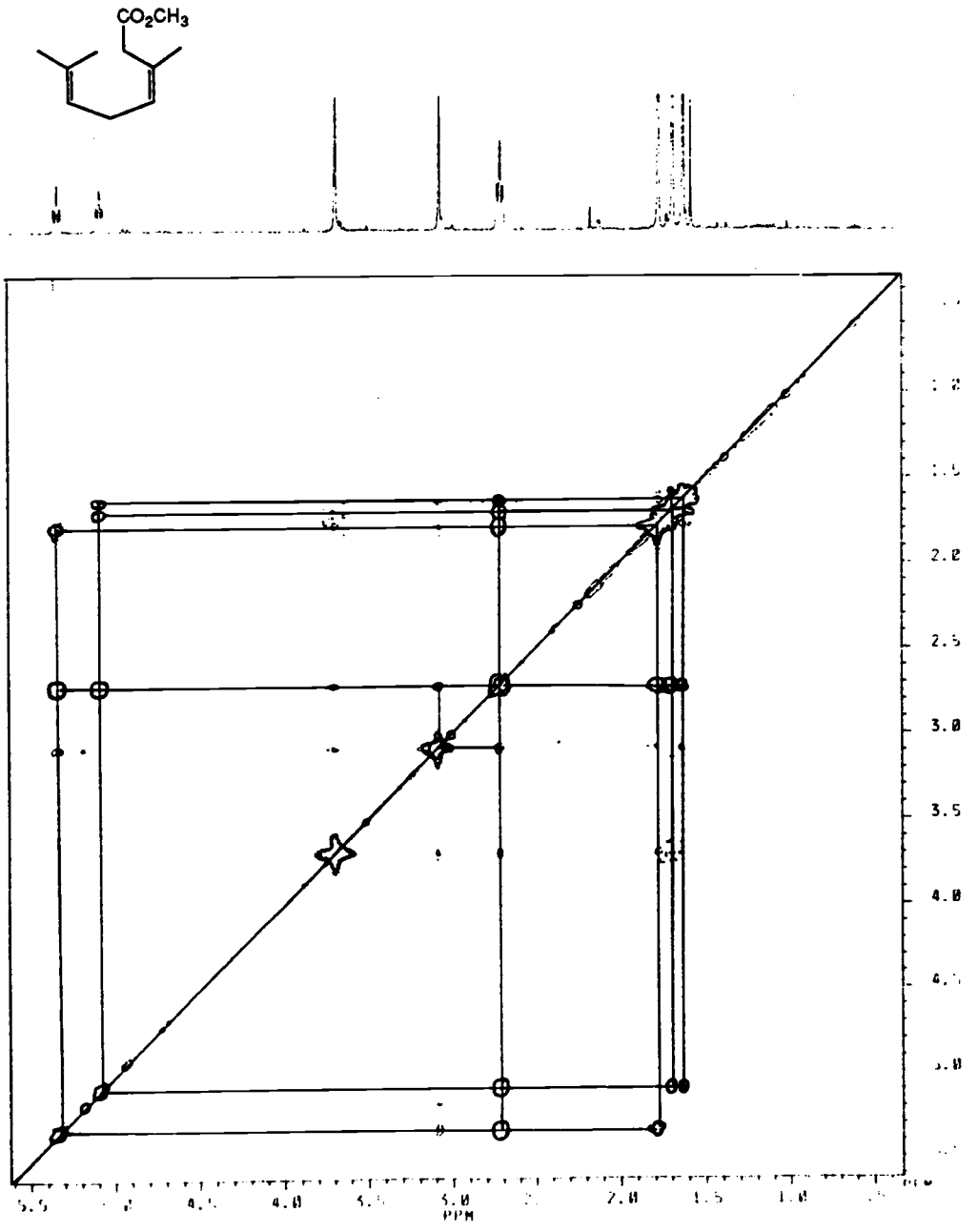


Figure 9. ^{1}H-COSY45 Spectrum of Methyl (3E)-3,7-Dimethyl-3,6-octa dienoate, 101.

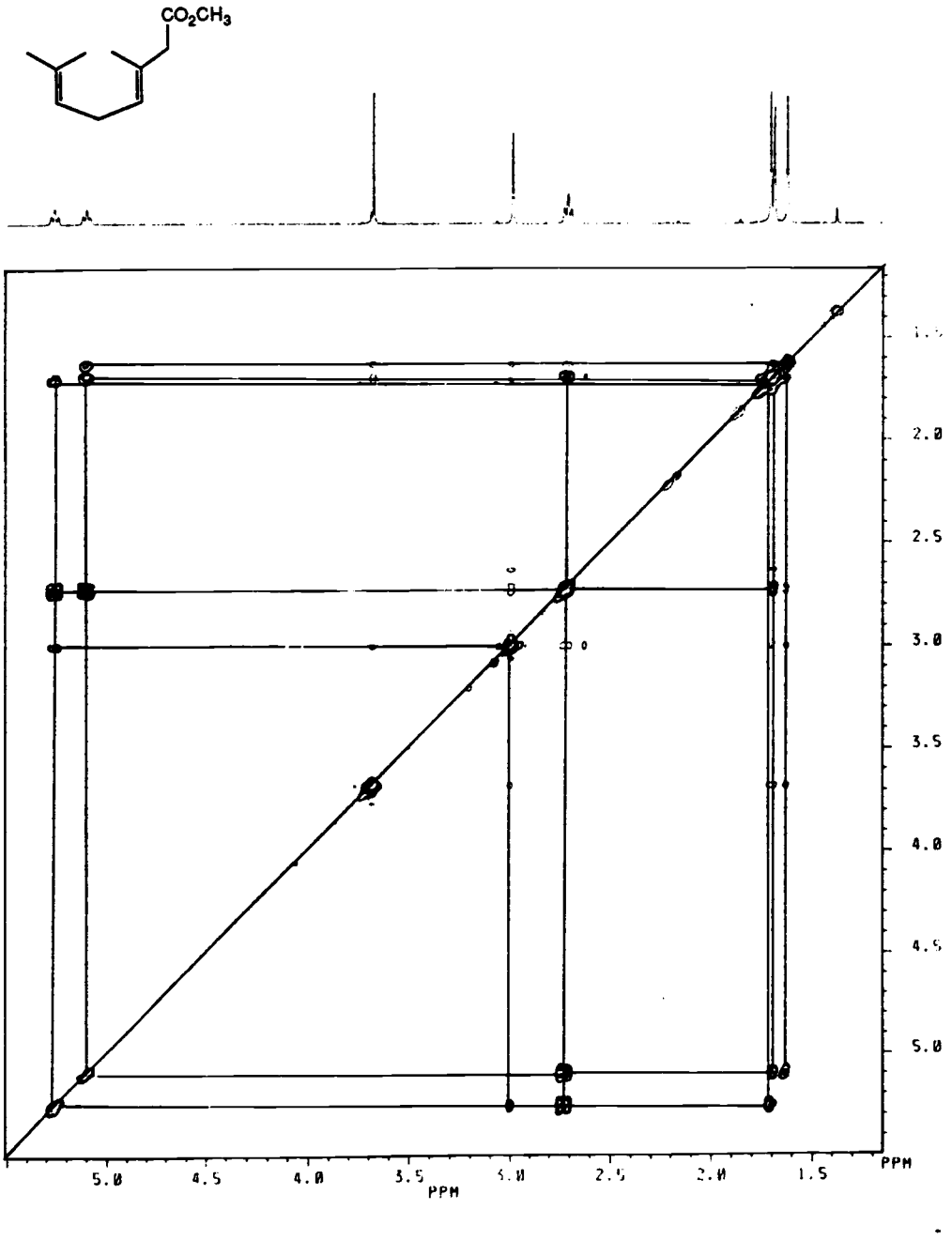


Figure 10. ^{1}H, ^{13}C-HETCOR Spectrum of Methyl (3Z)-3,7-Dimethyl -3,6-octadienoate, 100.

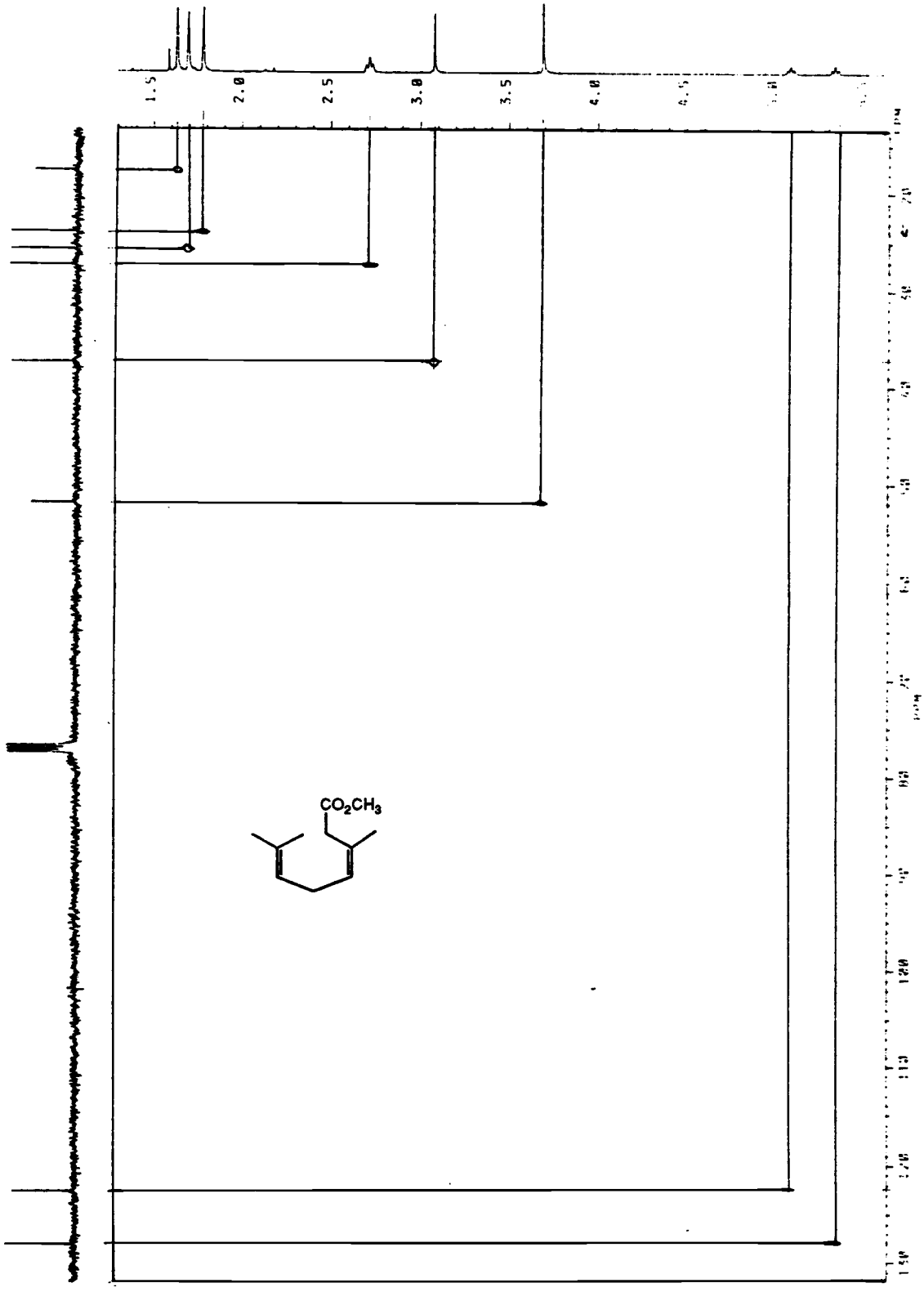
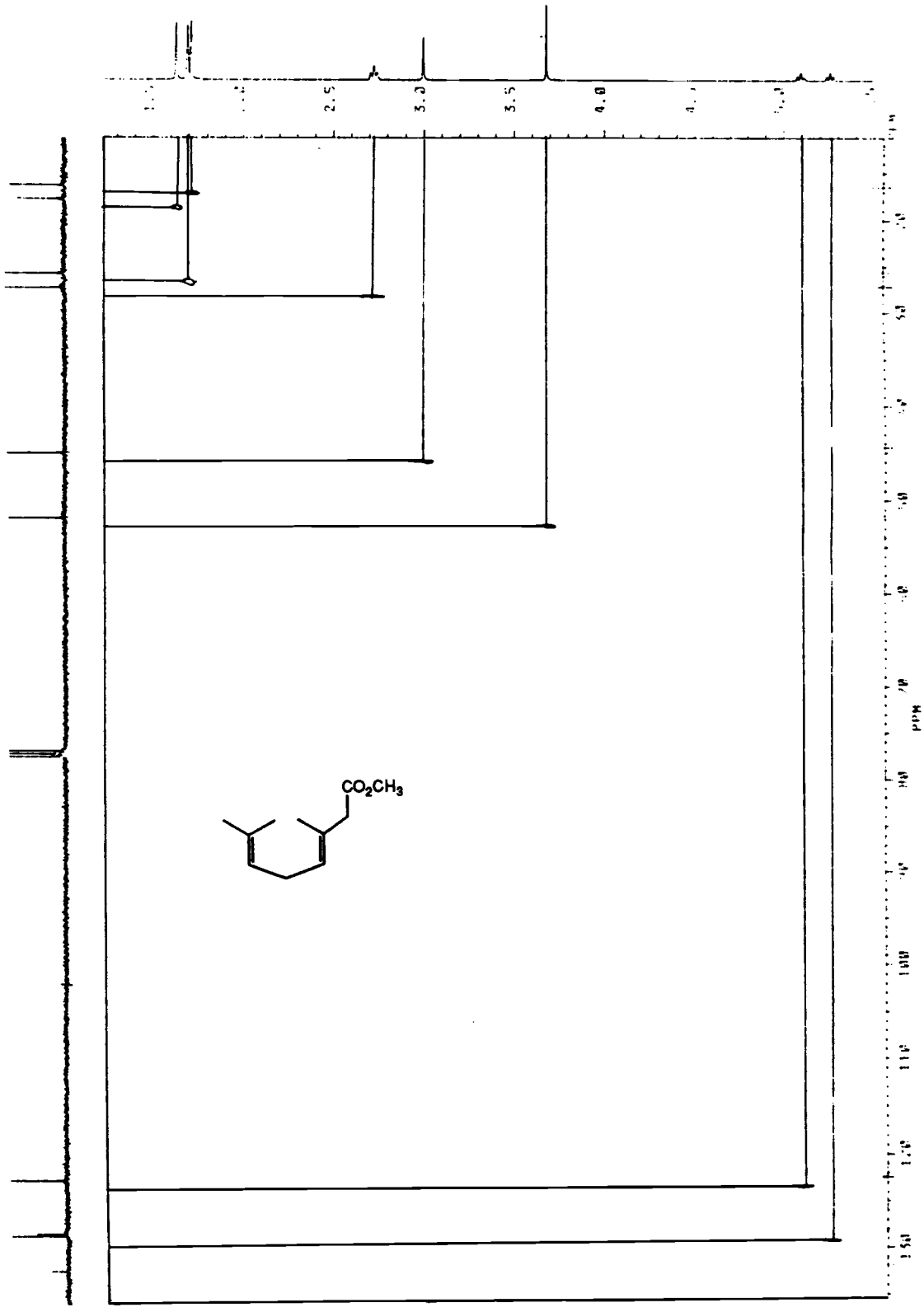


Figure 11. ^{1}H, ^{13}C-HETCOR Spectrum of Methyl (3E)-3,7-Dimethyl -3,6-octadienoate, 101.



to C-3, which shifts downfield by 7.6 ppm. This demonstrates a shielding effect on carbons cis to the isoprenyl group and the magnitude of the shielding appears to be insensitive to the primary or secondary nature of the carbon. This effect also manifests itself in simple trisubstituted alkenes.[45] In 2-methyl-2-butene the carbon attached to C-2 that is cis to the carbon attached to C-3 is shifted upfield by 8.4 ppm. Erman also noted that the glc retention time of 100 is several minutes shorter than 101 (20% Reoplex 400 on Anakrom ABS 300, 60/80 mesh); this is the same behavior exhibited in our glc studies using an OV-17 column. The observation that cis isomers elute faster than trans isomers of unsaturated hydrocarbon or terpenoid compounds is a trend that this author has noted in many sources, on many E/Z isomer systems.[53,54] It is not expected that the two peaks would reverse their order of elution in going from the Reoplex 400 column to the OV-17 column since their polarities are similar (Reoplex 400 is a polyethyleneglycol adipate and OV-17 is a 50% methyl, 50% phenyl silicone oil, and both are activity (polarity) type III [55]).

Before a detailed study of the mechanistic pathways involved in the irradiation of methyl geranate, 71, was undertaken an irradiation of 71 in water was run. The purpose of this irradiation was to quickly assess the environmental significance of any subsequent irradiations done in ether. The results of irradiations in ether and water are summarized in Table 1. The points to note are that in water all the same products are formed, but the reaction seems to go faster (greater loss of starting material after eight hours in water) and there is an increased formation of deconjugation products.

After the identity of the products formed during the photolysis of methyl geranate were unambiguously determined, the process of determining the mechanistic pathways leading to the formation of each of those products was undertaken. The results of an irradiation time vs relative composition experiment for 71, with 254 nm lamps, are summarized in figure 12. Composition vs time curves are plotted for 98, 72, 73, 100, 97 and 71. The notable features of figure 12 is the

Table 1. Relative composition of Photolysis Products From Direct Irradiation of Methyl Geranate in Ether and Water.

	Relative Composition							
solvent	98	72	73	99	100	97	101	71
ether[a]	1.00	1.78	2.18	0	1.61	33.2	0	33.7
water[b]	1.00	2.18	2.48	1.84	3.75	18.1	3.06	22.2

a) 254 nm lamps

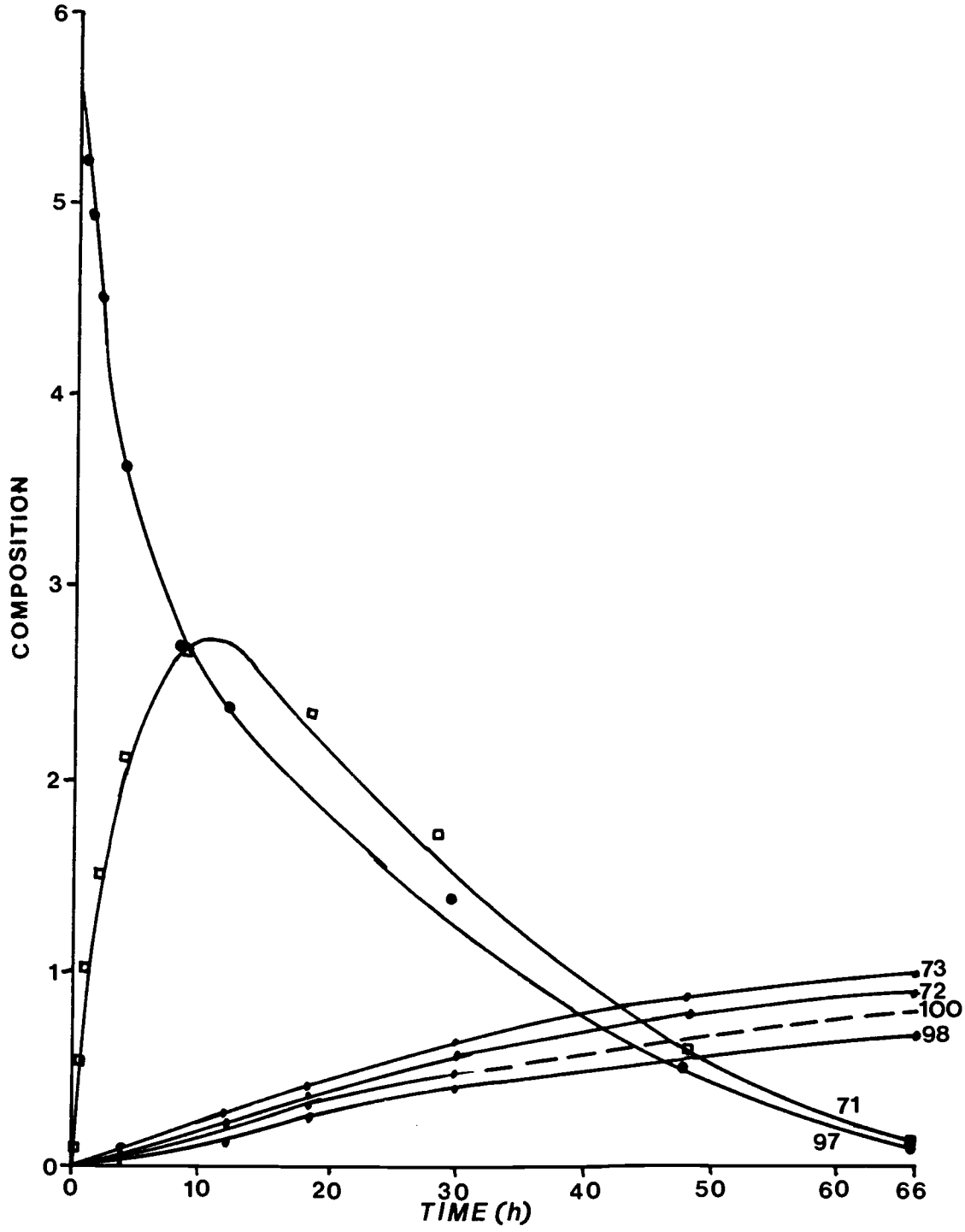
b) Hanovia 450 watt, medium pressure, mercury arc lamp

rapid photoequilibration of 97 and 71, relative to the formation of 98, 72, 73 and 100. The ratio of 97/71 is 1.23 after photoequilibrium has been reached and this ratio does not change, even out to 48 h.

Earlier in the course of this project an irradiation time vs relative composition (of methyl geranate photolysis products) experiment was carried out with a Hanovia 450 Watt, medium pressure mercury arc lamp and the results are shown in figure 13. This study differed from the one just discussed, with the 254 nm lamps, in that trace base sources were not scrupulously excluded and photodeconjugation to 99, 100 and 101 becomes the predominant pathway. The features to note in Figure 13 are that photoequilibrium, with 97 predominating slightly, is established after approximately 12 h and that the loss of 97 and 71 again parallel each other. The increased yield of deconjugation products does not effect the E/Z equilibrium since it is fast relative to the deconjugation process.

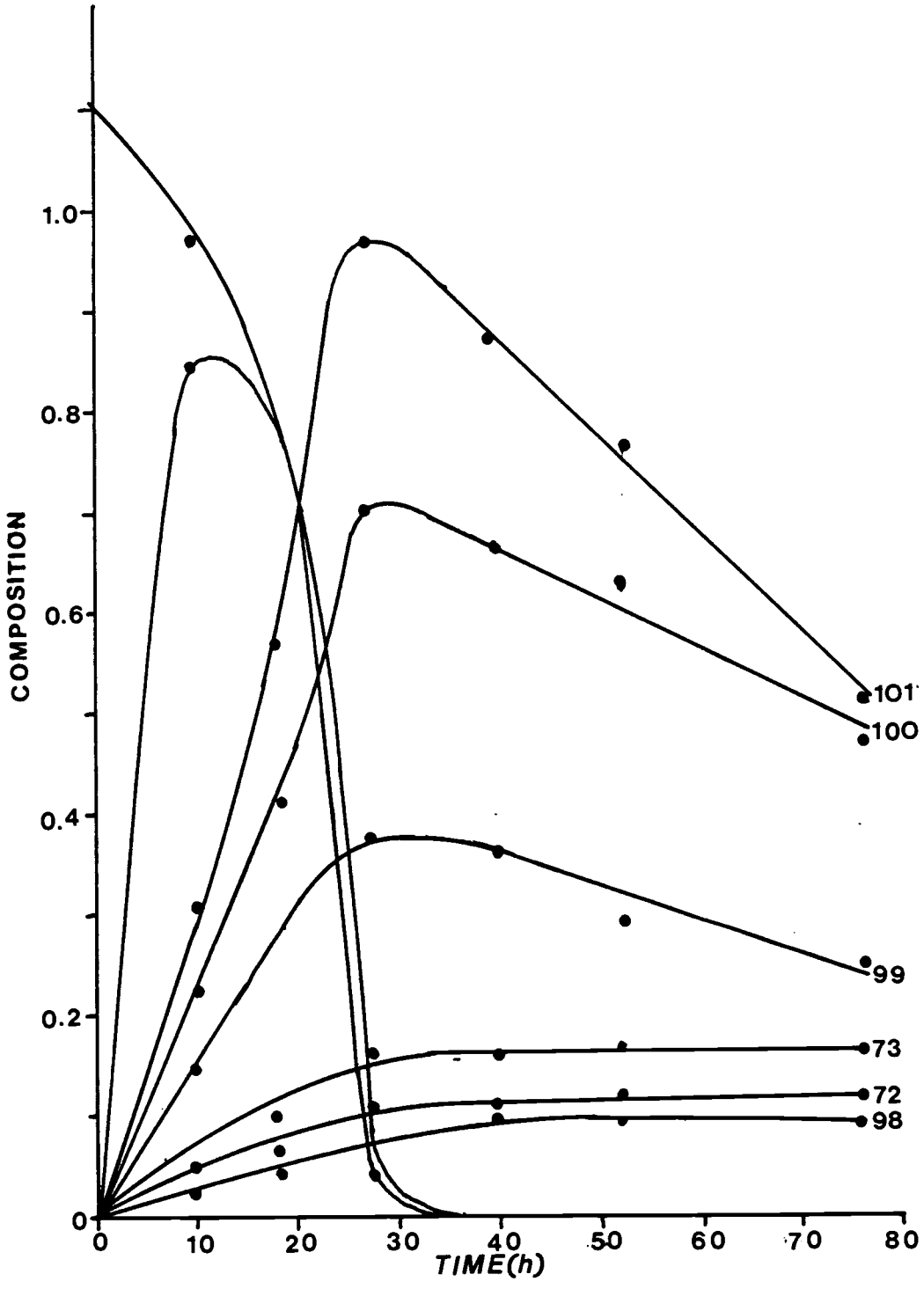
In order to begin elucidation of the mechanism(s) for the formation of the methyl geranate photolysis products, 71 was irradiated in the presence of various triplet sensitizers of increasing triplet energy, under conditions where the sensitizers absorbed >95% of the incident light. Table 2 summarizes the results of those experiments and Scheme 28 presents a simple rationale to explain the origin of the

Figure 12. Irradiation Time Vs Relative Composition[a] for Methyl Geranate in Ether at 254 nm.



a. Composition is relative to internal standard (dodecane).

Figure 13. Irradiation Time vs Relative Composition[a] for Methyl Geranate in Ether with a Hanovia 450 Watt Medium Pressure Lamp.



a. Composition reaalative to internal standard (dodecane).

products. In accordance with prior results on the triplet sensitized irradiation of methyl geranate, the only products formed are 72, 73 and 97.[24] The photochemical E/Z isomerization of α,β-unsaturated esters had previously been shown to be a triplet process by Barltrop, et. al.[10] and Jorgenson.[7]

Use of acetophenone as the triplet sensitizer proved to be inconvenient. Under the glc conditions used for the analysis of the photolysis mixtures, acetophenone and 98 both had identical retention times. Thus, analysis for 98 was rendered impossible. Carrying out the reaction with propiophenone as the triplet sensitizer solved this problem since the retention time of propiophenone was greater than that of 73 (the third component to elute from the gas chromatograph). With the use of propiophenone as triplet sensitizer it was possible to look for the formation of 98, but none was detected in any of the irradiations, thus showing conclusively that it is not formed from a triplet intermediate. Scheme 28 shows the spin state responsible for the formation of each product formed in the irradiation of 71. The triplet intermediate, T_1, has the same structure wheather it is formed from either 71 or 97 and the rate of triplet product formation is the same from this intermediate whether formed from 71 or 97

Scheme 28

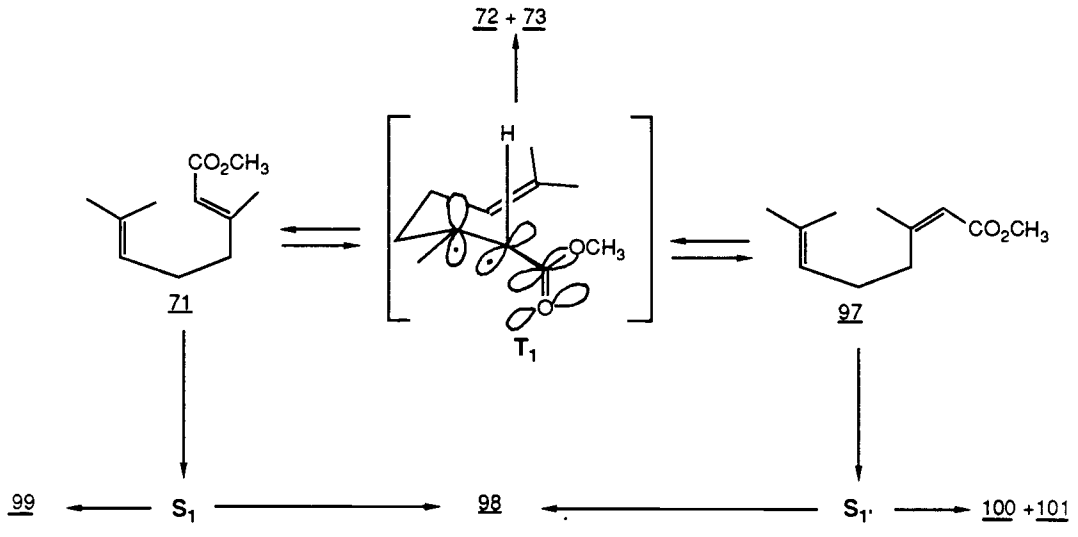


Table 2. Product Distribution vs Triplet Energy of the Sensitizer.

Sensitizer	Triplet Energy[a] (kcal/mol)	$\varepsilon_{254\ nm}$[a]	Products
Acetophenone	74.1	6×10^3	72, 73, 97
Propiophenone	74.5	5×10^3[b]	72, 73, 97
Benzene	84.3	9×10^1	72, 73, 97

a) Murov, S.L. "Handbook of Photochemistry" Marcel-Dekker, 1973

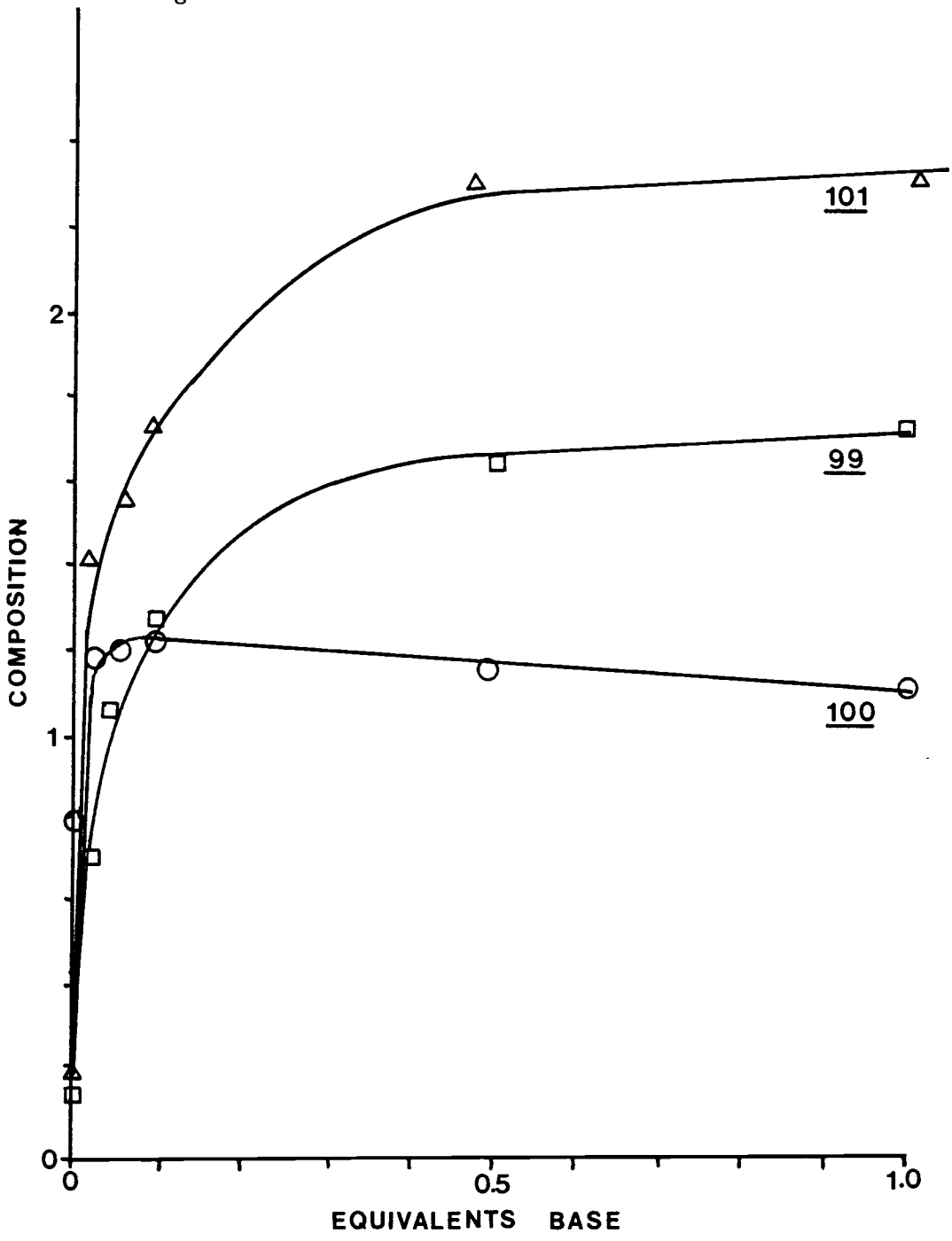
b) estimates from the value for butyrophenone; $\varepsilon_{254} = 5 \times 10^3$

If 71 was irradiated with the scrupulous exclusion of any base sources (in the solvent or on the quartz tube walls) then the only photodeconjugation product formed, in small amounts, is 100 (approximately 6% of the photolysis mixture after 18 h of irradiation). Addition of a weak, non-nucleophilic base, 1,2-dimethylimidazole (1,2-DMI), completely alters the course and product distribution of the irradiations. Figure 14 summarizes the results of irradiation of 71 in ether with varying amounts of 1,2-DMI. After addition of 0.5 equivalent of 1,2-DMI has been added the composition of 99 and 101 are at constant levels, which are unaffected by additional base. The composition of 100 reaches a plateau after the addition of only 0.02 equivalent of 1,2-DMI. Figure 15 represents the ratios 100/99 and 101/99. The two things to note in this plot are that the ratio 100/99 reaches a constant value after the addition of approximately 0.5 equivalent of 1,2-DMI and the ratio 101/99 is constant from 0.01 equivalent and greater.

Weedon et al have done the most extensive studies on the photochemical deconjugation reaction of simple α,β-unsaturated ketones and esters (see discussion in the introduction pp 9-11).[11-15] The difference between prior work and this current study on the mechanism and kinetics of photodeconjugation is that we have developed our kinetic expressions using an intramolecular competitive reaction scheme. This approach takes advantage of the isolated double bond at C-6 and its participation in the cyclization reaction to 73. The proposed mechanism for the formation of 72, 73 and 97-101 is presented in its complete form in Scheme 29.

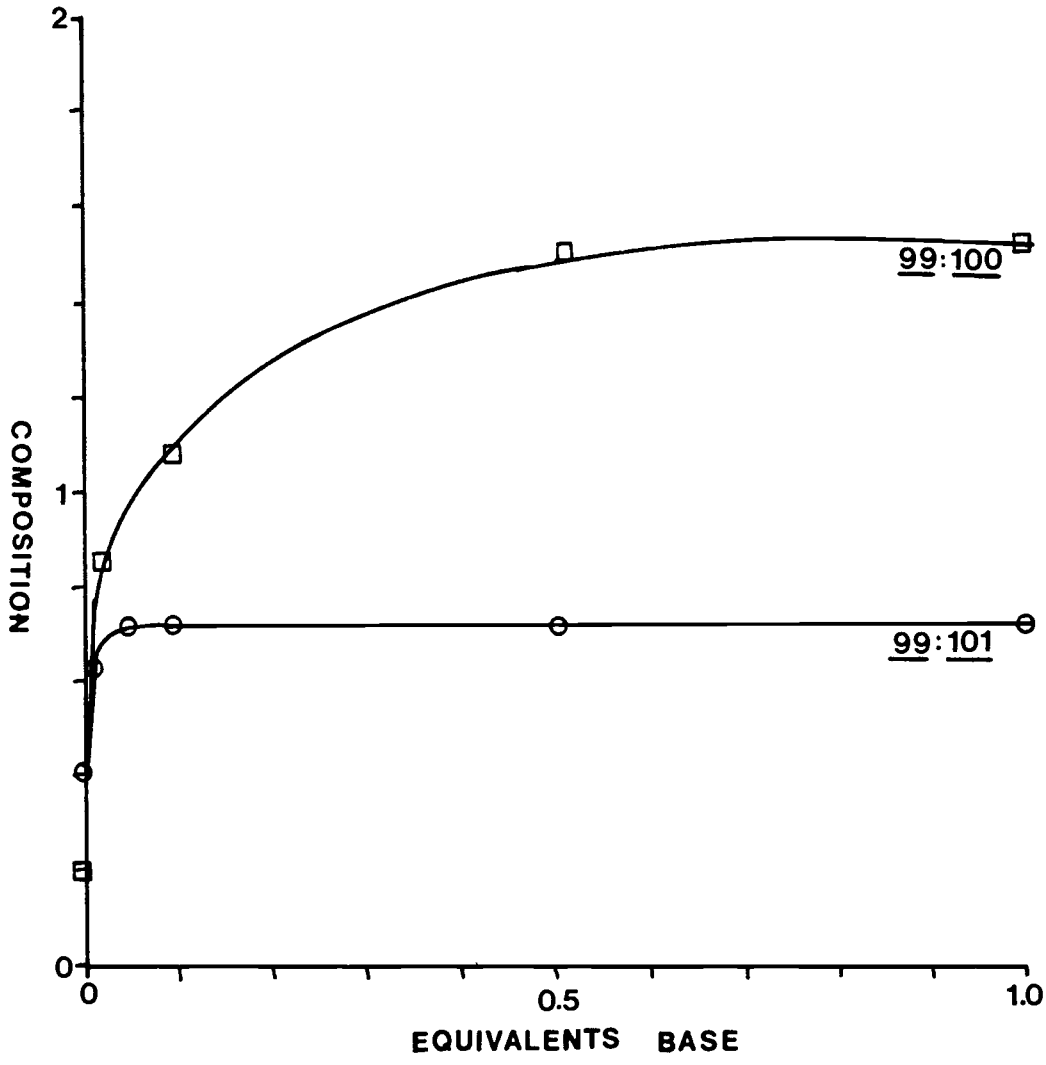
Irradiation of 71 with 254 nm light generates an excited singlet species, S_1, and this intermediate can undergo one of three reactions. A [1,3] sigmatropic shift of the prenyl group to form 98, the least abundant product during any of the irradiations carried out. The S_1 species also undergoes facile intersystem crossing to the triplet species T_1, which is the species to undergo rapid isomerization of the C-2 double bond to form 97. T_1 also forms 72 and 73 through a common diradical intermediate which was discussed earlier. Isolation and separation of 98, 72, 73 and 99 by preparative

Figure 14. Equivalents of 1,2-DMI vs Relative Composition[a] for Irradiation of Methyl Geranate in Ether for 8 h with 254 nm Light.



a. composition is relative to internal standard (dodecane)

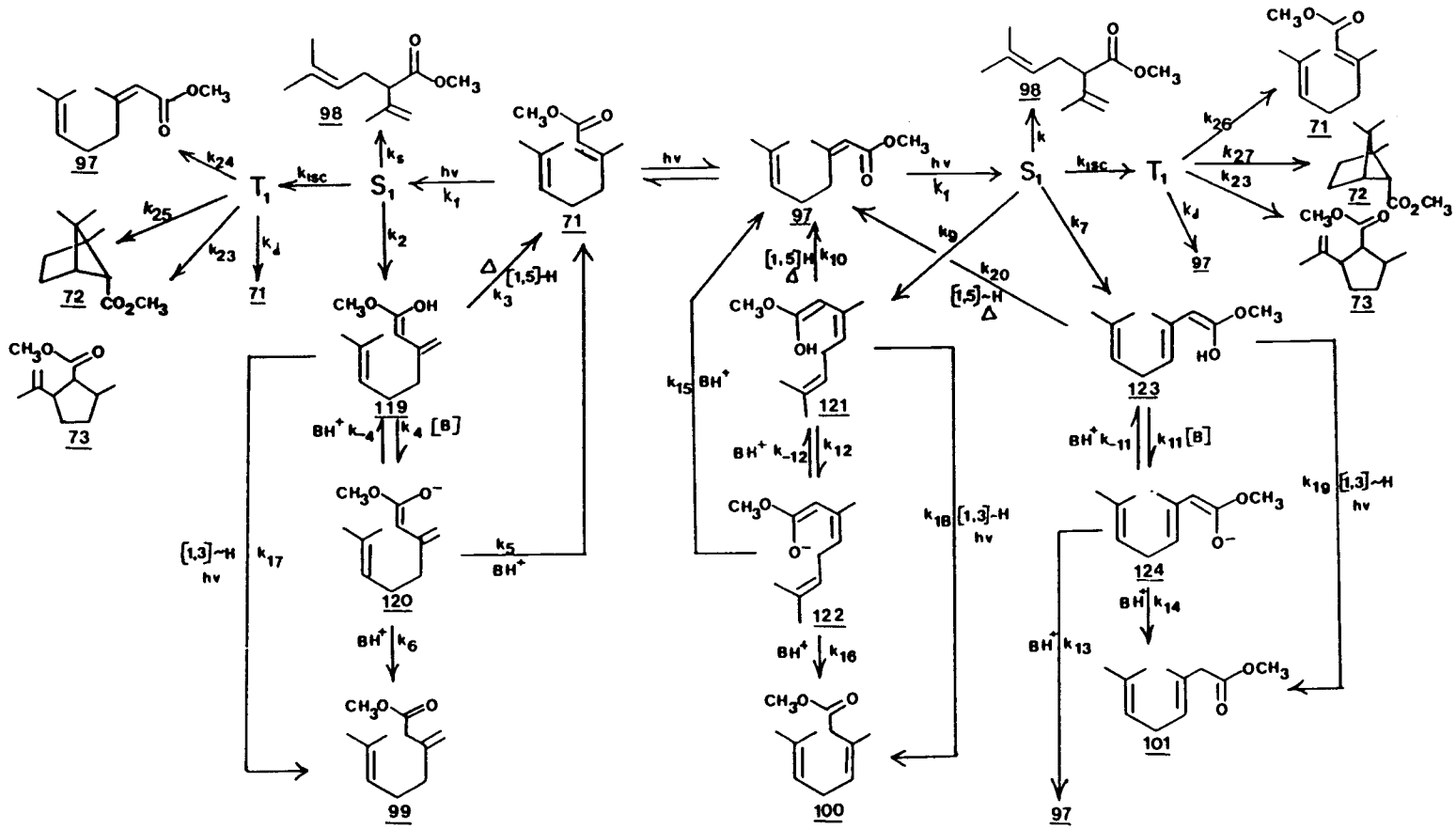
Figure 15. Ratios of 99/100 (and 99/101) vs Equivalents of 1,2-DMI for Irradiation of Methyl Geranate in Ether for 8 h with 254 nm light.



glc, followed by irradiation of each in ether for 9 h demonstrated that these are all inert to further photochemical reaction and do not re-enter the reaction manifold. Using the model of Weedon for the deconjugation to 99, S_1 forms the photoenol by an intramolecular hydrogen abstraction reaction, k_2, to form the photodienol 119. This dienol has three reaction paths available. First, a [1,3] hydrogen shift, k_{1_7}, which is an allowed suprafacial process for an excited state by the Woodward-Hoffmann rules, would generate 99. This is not a significant reaction since it is independent of added base and it has been shown that without added base 99 is not formed in any but trace amounts. Second, if no base is present in the reaction, then a ground state [1,5] sigmatropic shift of hydrogen, k_3, would regenerate starting material 71. This has been shown to be the predominant pathway in analogous esters and ketones when no base is present,[11-15] giving the impression of photoinertness. However, if base is added to the photolysis, the photodienol 119 can be deprotonated on oxygen to form photodienolate anion 120. Once formed, 120 can be reprotonated at one of three locations, on oxygen to regenerate 119 or on either the alpha or gamma carbons. Using ordinary enolate chemistry analogies, with the available proton sources in solution to reprotonate the dienolate, alpha (kinetic) reprotonation would be the expected pathway.[56] 1,2- dimethyl-imidazole ($pK_a \simeq 7.5$) was used in these irradiations because it is soluble in the solvent chosen (ether), and even though it is a strong enough base to deprotonate the photodienol 119, it is not a strong enough base to deprotonate 99 and move the double bond back into conjugation. Gamma reprotonation of 120 would regenerate 71. Gamma reprotonation, under the reaction conditions used, would not be expected to be the major reaction pathway.

Two assumptions (observations) are made prior to deriving the rate expressions for this reaction manifold. First, isomerization of 71 and 97 is a rapid process relative to formation of any other products, so a photoequilibrium is set up fairly rapidly (see Figure 12) and second, formation of 72, 73, 98 and 99 is irreversible.[57] Based on Scheme 29 it is possible to derive a kinetic expression, Scheme 30,

Scheme 29


97
98
71
72
73
119
120
99
121
122
100
123
124
101
hv
k_1
k_2
k_3
k_4
k_5
k_6
k_7
k_9
k_{10}
k_{11}
k_{12}
k_{13}
k_{14}
k_{15}
k_{16}
k_{17}
k_{18}
k_{19}
k_{20}
k_{23}
k_{24}
k_{25}
k_{26}
k_{27}
k_d
k_{isc}
k_s
k_{-4}
k_{-11}
k_{-12}
[B]
BH^+
[1,5]-H
[1,3]-H
Δ

for the formation of 73 vs 99 (as well as expressions for 73 vs 100 and 73 vs 101) based on ratios of relative quantum yields for formation of 73 and 99, 100 and 101. The derivation is shown in full in Scheme 30 and the results are summarized in Table 3.

Based on equation 9, a plot of 73/99 (relative yields from glc analysis) vs $[1,2\text{-DMI}]^{-1}$ should yield a straight line with the slope and intercept given by the quantities in equation 10 . This plot is presented in Figure 16 and shows the predicted straight line with good correlation, r = 0.995. Similar plots can be made of 73/100 and 73/101 vs $[1,2\text{-DMI}]^{-1}$, Figures 18 and 17 respectively. In the case of equation 10, dividing the slope by the intercept leaves the quantity $(k_3 + k_{17})(k_{-4}+k_5+k_6)/ k_4k_6M$. k_{-4}, k_5 and k_6 are the rate constants for reprotonation of the photodienolate and it seems reasonable to assume that the ration of these will be approximately the same for the three different photodienolate species (120, 122 and 124). So equation 11 simplifies to approximately k_3/k_4, or simply the rate constant for [1,5] sigmatropic shift divided by the rate constant for dienol deprotonation (assuming that k_{17} is small). A similar analysis can be made for 73/100 and 73/101 versus $[1,2\text{-DMI}]^{-1}$ from Scheme 29, Figures 18 and 17 respectively. The results are presented in table 3.

The ratio of rate constants for the deconjugation to 99 and 101 are very close, 5.26×10^{-3} and 6.23×10^{-3} respectively, while the same ratio is on the order of 75 times smaller for 100, 7.30×10^{-5}. Assuming that the rate of dienol deprotonation is the same for all three dienols, 119, 121 and 123, then the values for the slope/intercept of the lines in Figures 16-18 can be used to estimate the relative rates for the ground state [1,5] hydrogen shift from the dienol to regenerate starting material, 71 or 97. The relative rates for this [1,5] shift are 72, 85 and 1.0 for dienols 119, 123 and 121, respectively. The rates for 119 and 123 can be considered to be essentially the same in the context of this discussion, relative to 121, which is slower by a factor of about 75. Examination of the dienol structures in Scheme 33 reveals that dienol 121, when in the s-cis conformation, is in a sterically unfavorable conformation and

Scheme 30

For the formation of 99:
From Scheme 29 assume that $k_{17} << k_4[B]$ and 119 and 120 are at steady state concentrations

$$[\underline{119}]_{ss} = \frac{k_1[\underline{71}] \cdot \frac{k_2}{k_2+k_s+k_{isc}} + k_{-4}[BH^+][\underline{120}]}{k_3+k_4[B]} \qquad (1)$$

$$\text{Let } P = \frac{k_2}{k_2+k_s+k_{isc}}$$

$$[\underline{120}]_{ss} = \frac{k_4[\underline{119}][B]}{[BH^+](k_{-4}+k_5+k_6)}$$

Substitute in Eqn. 1

$$[\underline{120}]_{ss} = \frac{k_4[B]}{[BH^+](k_{-4}+k_5+k_6)} \cdot \frac{k_1[\underline{71}] \cdot P + k_{-4}[BH^+][\underline{120}]}{k_3+k_4[B]}$$

$$= \frac{Pk_4k_1[\underline{71}][B] + k_4k_{-4}[\underline{120}][B][BH^+]}{[BH^+](k_{-4}+k_5+k_6)(k_3+k_4[B])}$$

$$\text{Let } R = [BH^+](k_{-4}+k_5+k_6)(k_3+k_4[B]) \qquad (2)$$

Scheme 30 (cont.)

$$[\underline{120}]_{ss} - \frac{k_4 k_{-4}[\underline{120}][B][BH^+]}{R} = \frac{P\, k_4 k_1 [\underline{71}][B]}{R}$$

$$[\underline{120}]_{ss} \frac{\{R - k_4 k_{-4}[B][BH^+]\}}{R} = \frac{P\, k_4 k_1 [\underline{71}][B]}{R}$$

Substituting back in Equation 2 for R and rearranging:

$$[\underline{120}]_{ss} = \frac{P\, k_4 k_1 [\underline{71}][B]}{[BH^+]\ \{\ (k_{-4}+k_5+k_6)(k_3+k_4[B]) - k_4 k_{-4}[B]\ \}} \qquad (3)$$

Then from Scheme 29

$$\frac{d[99]}{dt} = k_6 [\underline{120}][BH^+] \qquad (4)$$

and

$$\Phi_{\underline{99}} = \frac{\frac{d[99]}{dt}}{k_1 [\underline{71}]}$$

Substitute in Equations (3) and (4) then simplify

$$\Phi_{\underline{99}} = \frac{P\, k_6 k_4 [B]}{(k_{-4}+k_5+k_6) \cdot (k_3+k_4[B]) - k_4 k_{-4}[B]}$$

Scheme 30 (cont.)

For the formation of 73:
From Scheme 29 assume that S_1 and T_1 are at steady state

$$[S_1]_{ss} = \frac{k_1[71]}{k_s+k_{isc}+k_2} \tag{5}$$

$$[T_1]_{ss} = \frac{k_{isc}[S_1]}{k_{23}+k_{24}+k_{25}+k_d}$$

Substitute in for $[S_1]$

$$[T_1]_{ss} = \frac{k_{isc}}{k_{23}+k_{24}+k_{25}+k_d} \cdot \frac{k_1[71]}{k_s+k_{isc}+k_2} \tag{6}$$

$$\frac{d[73]}{dt} = k_{23}[T_1]$$

and

$$\Phi_{73} = \frac{\frac{d[73]}{dt}}{k_1[71]} = \frac{k_{23}[T_1]}{k_1[71]}$$

Substitute in Equation (6) and simplify to get the amount of 73 formed from the left half of the reaction manifold.

$$\Phi_{73} = \frac{k_{23}}{k_{23}+k_{24}+k_{25}+k_d} \cdot \frac{k_{isc}}{k_{isc}+k_s+k_2}$$

Add on to $\Phi_{\underline{73}}$ the amount of $\underline{73}$ formed from the right half of the reaction manifold then:

$$\Phi_{\underline{79}} = \frac{k_{isc}}{k_2+k_s+k_{isc}} \cdot \frac{k_{23}}{k_{23}+k_{24}+k_{25}+k_d} + \frac{k_{isc}}{k_{isc}+k_s+k_7+k_9} \cdot \frac{k_{23}}{k_{23}+k_{26}+k_{27}+k_d} \cdot E \tag{7}$$

Where E = a proportionality factor to correct for k and the different ϵ of $\underline{97}$.

$$\frac{\Phi_{\underline{99}}}{\Phi_{\underline{73}}} = \frac{(\underline{99})}{(\underline{73})} = \frac{\frac{k_2}{k_2+k_s+k_{isc}} \left\{ \frac{k_6k_4[B]}{(k_{-4}+k_5+k_6)(k_3+k_4[B]-k_4k_{-4}[B]} \right\}}{\frac{k_{isc}}{k_2+k_s+k_{isc}} \cdot \frac{k_{23}}{k_{23}+k_{24}+k_{25}+k_d} + \frac{k_{isc}}{k_{isc}+k_s+k_7+k_9} \cdot \frac{k_{23}}{k_{23}+k_{26}+k_{27}} \cdot E} \tag{8}$$

$$\frac{(\underline{99})}{(\underline{73})} = \frac{\frac{k_2}{k_2+k_s+k_{isc}} \left\{ \frac{k_6k_4[B]}{(k_{-4}+k_5+k_6)(k_3+k_4[B]) - k_4k_{-4}[B]} \right\}}{\Phi_{\underline{73}}}$$

Let $M = \frac{1}{\Phi_{\underline{73}}} \cdot \frac{k_2}{k_s+k_2+k_{isc}}$

$$\frac{(\underline{73})}{(\underline{99})} = \frac{(k_5+k_6)}{Mk_6} + \frac{k_3(k_{-4}+k_5+k_6)}{M\,k_6k_4[B]} \tag{9}$$

This is of the form $y = mx+b$ where $y = \frac{(\underline{73})}{(\underline{99})}$ and $x = \frac{1}{[B]}$ Plot $\frac{(\underline{73})}{(\underline{99})}$ vs $\frac{1}{[B]}$

Scheme 30 (cont.)

$$\text{Slope} = \frac{k_3(k_{-4}+k_5+k_6)}{M\,k_6k_4} \text{ and intercept} = \frac{(k_5+k_6)}{M\,k_6} \tag{10}$$

$$\frac{\text{Slope}}{\text{Intercept}} = \frac{k_3(k_{-4}+k_5+k_6)}{k_4(k_5+k_6)} \tag{11}$$

Figure 16. Relative Quantum Yields of 73/99 vs $(1,2\text{-DMI})^{-1}$.

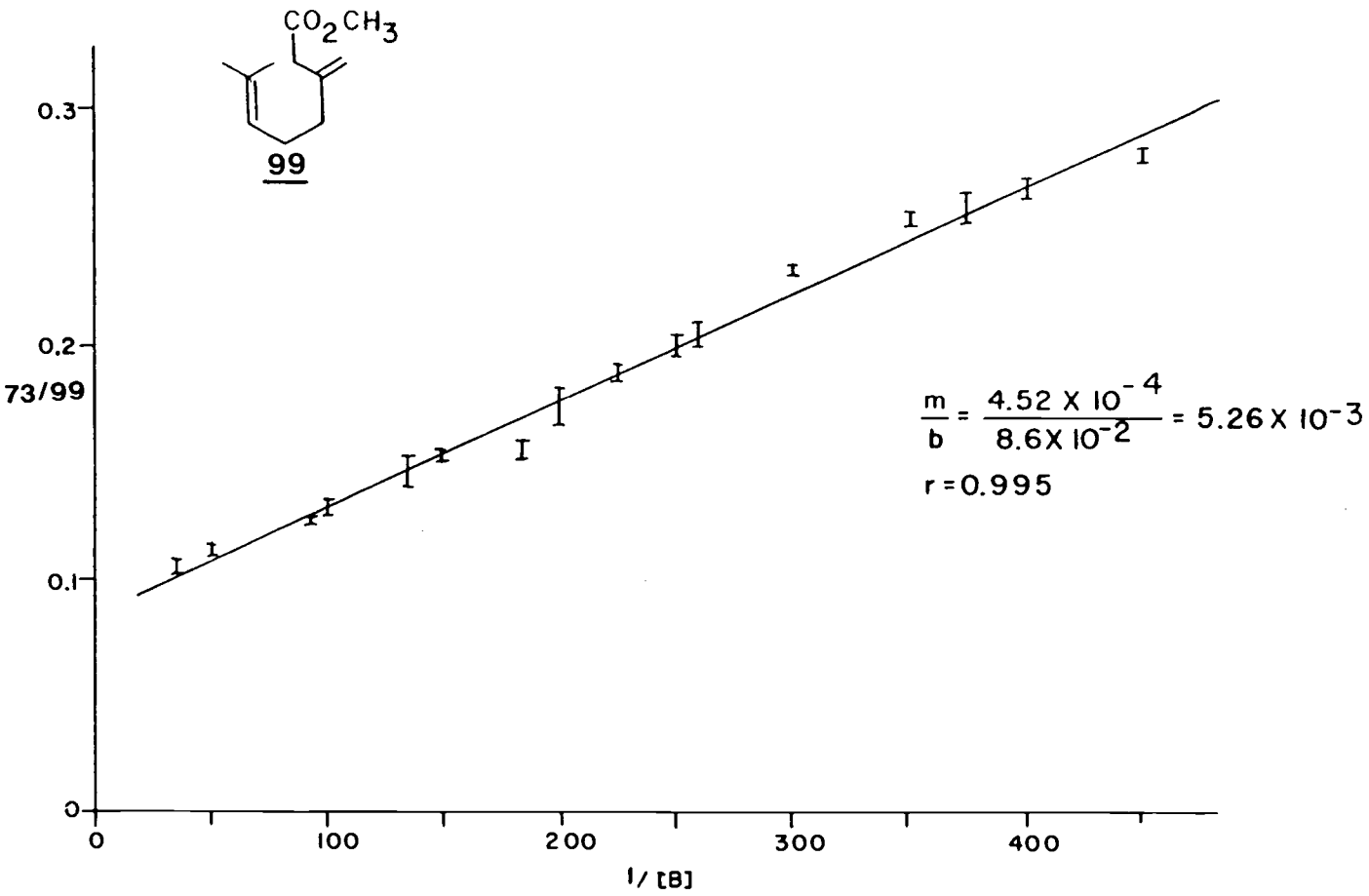


Figure 17. Relative Quantum Yield of 73/101 vs $(1,2\text{-DMI})^{-1}$.

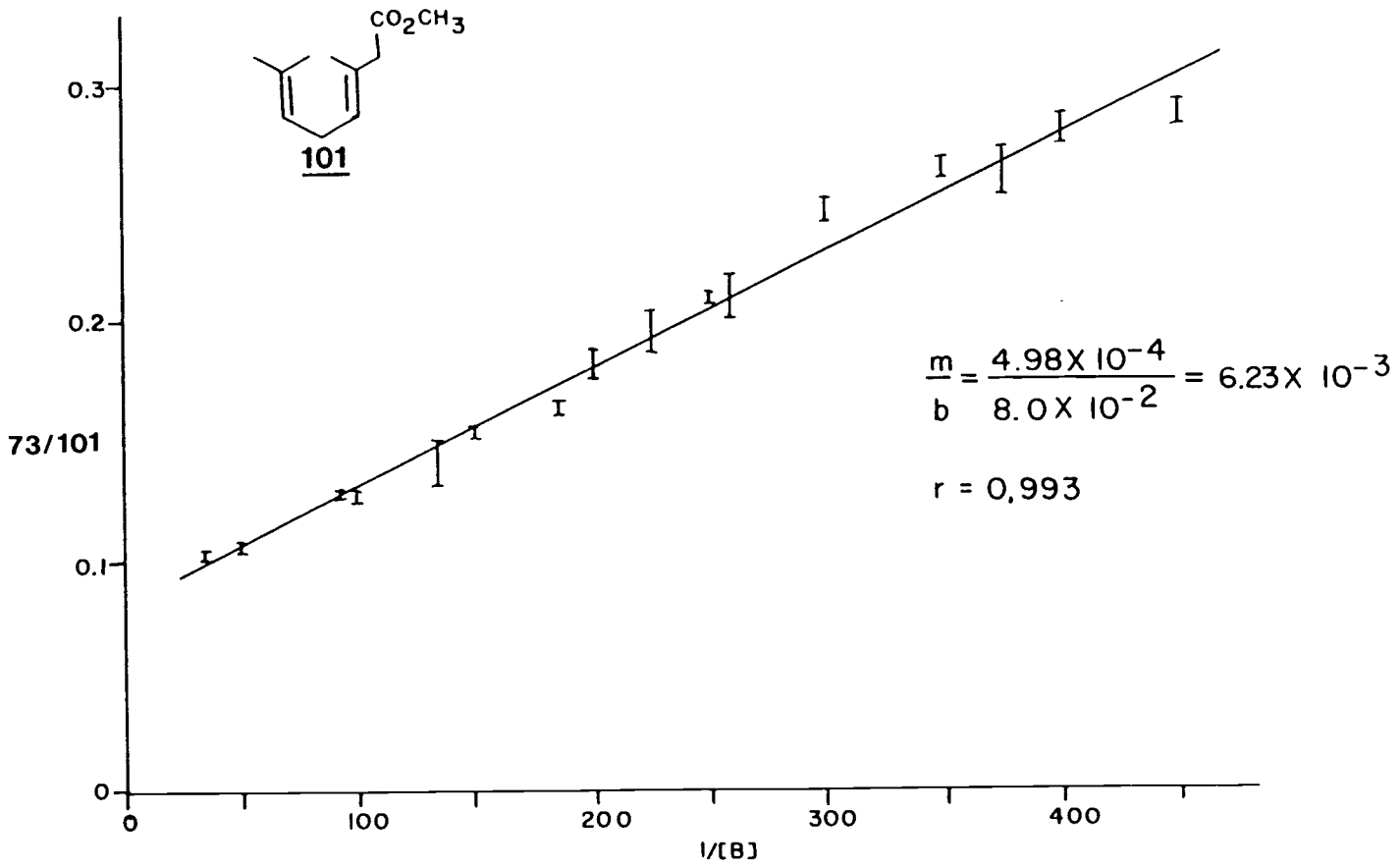


Figure 18. Relative Quantum yield of 73/100 vs $(1,2\text{-DMI})^{-1}$.

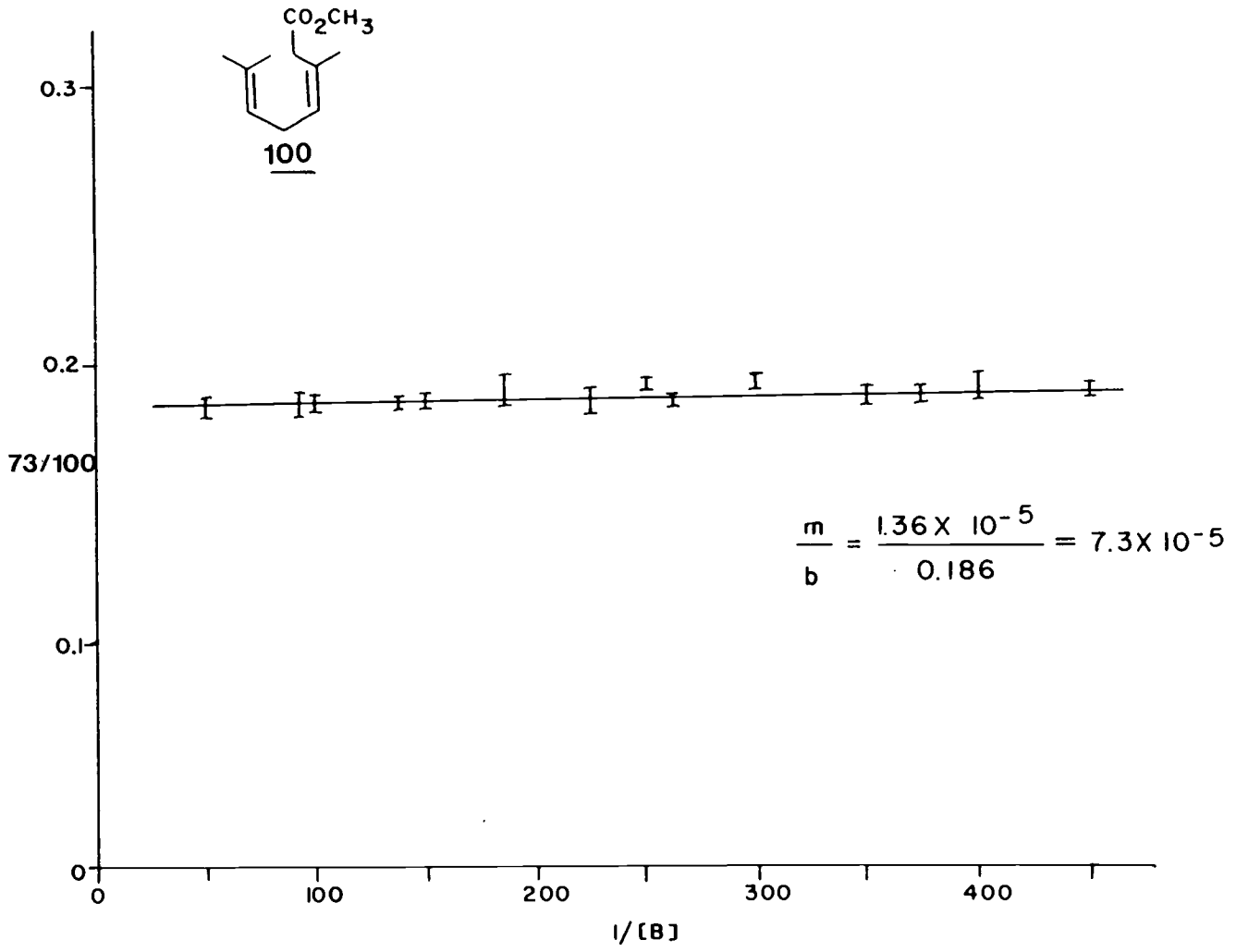


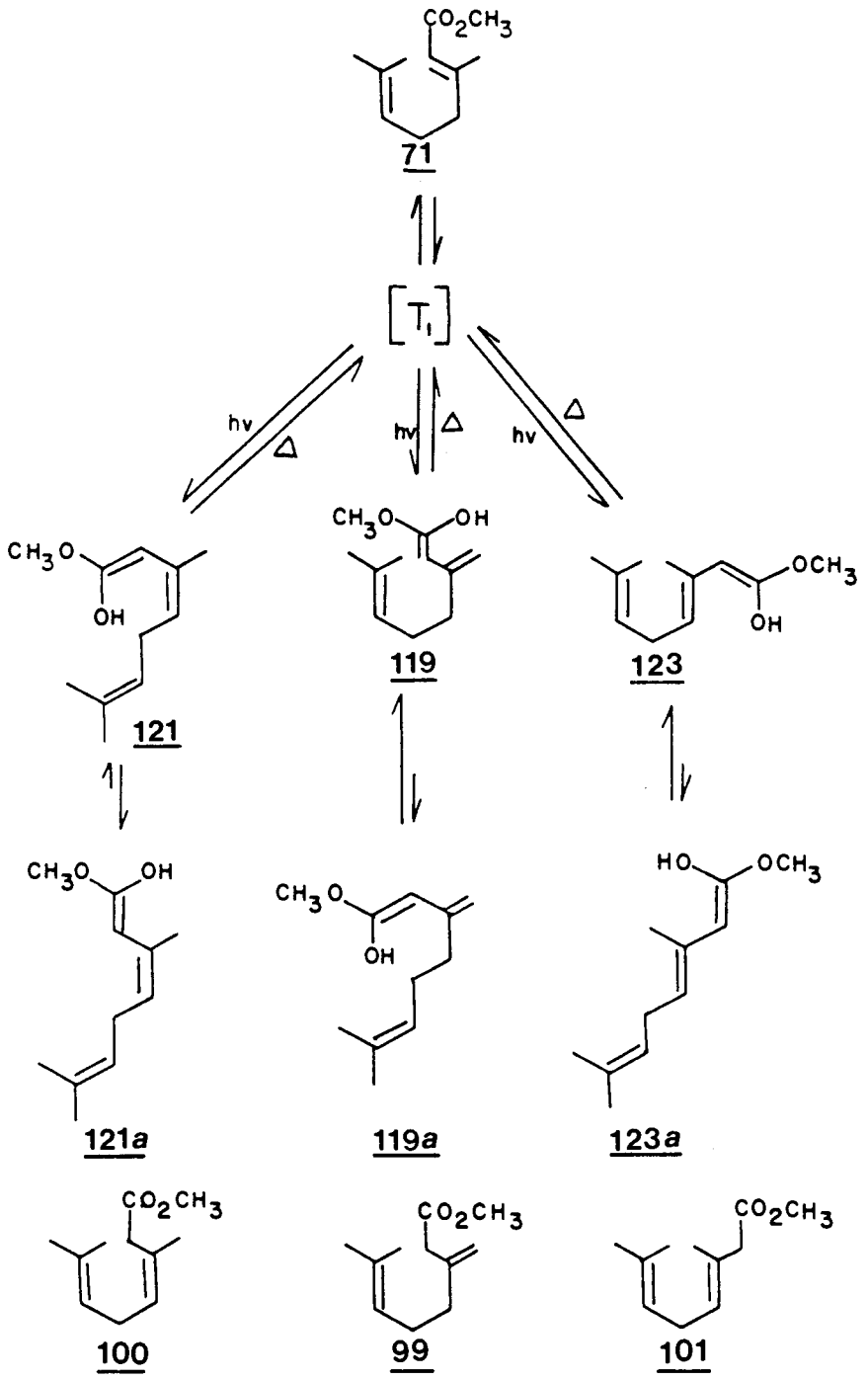
Table 3. Base Catalyzed Photodeconjugation Kinetics Results.

Compound	Slope	Intercept	$\frac{\text{Slope}}{\text{Intercept}}$	Relative Rate[a]
99	4.5×10^{-4}	8.6×10^{-2}	5.3×10^{-3}	1.00
100	1.4×10^{-5}	1.9×10^{-1}	7.3×10^{-5}	0.014
101	5.0×10^{-4}	8.0×10^{-2}	6.2×10^{-3}	1.18

a) Assumes that the rate of enol deprotonation is the same for all compounds, and rates are relative to 99.

rotation to the s-trans conformation, 121a, moves the dienol -OH away from the bulky prenyl group. Conversely, dienol structure 119 in the s-cis conformation, is more stable than if rotation to the s-trans conformation, 119a, takes place, putting the dienol -OH close to the bulky prenyl group. The case for dienol 123 is less clear-cut. Both the s-cis, 123, and the s-trans, 123a, conformations appear to have the same steric interactions when molecular models are examined. The s-cis conformation is the reactive conformation and all three dienols must adopt it for the [1,5] sigmatropic shift of the proton to be possible. Dienol 119 should prefer the s-cis conformation and dienol 123 should exist with a sustantial fraction adopting the s-cis conformation for the [1,5] shift. This is illustrated in the similar behavior that the final deconjugation products formed from these two compounds display in Figures 14 and 15. In Figure 14 the curves of 99 and 101 vs equivalents of 1,2-DMI both flatten out after the addition of about 0.5 equivalents of base, and in Figure 15, a plot of the ratio of 99/101 vs equivalents of 1,2-DMI, the curve flattens out to a slope of zero after the addition of only 0.02 equivalents of base. This shows that the reactivity of 99 and 101 are very similar with respect to the ratio of rates of enol deprotonation and [1,5] sigmatropic shift for each species. The near identical behavior of dienols 119 and 123 contrasts sharply with that of dienol 121. As stated above the most stable conformation for the dienol is 121a rather than 121; this rotates the -OH away from the bulky prenyl group and minimizes the unfavorable steric interaction. However, adoption of the s-trans conformation makes the [1,5] shift reaction impossible, and thus the relative rate for this process is significantly lower than that of 119 or 123 (slower by a factor of about 75). This is illustrated in Figure 14 by the flat slope achieved after the addition of only 0.02 equivalents of 1,2-DMI, the small amount of dienol that does undergo the [1,5] shift back to 97 is easily trapped as the dienolate by very little added base. The retardation of the [1,5] shift process for 121 relative to 119 or 123 also explains the results of direct irradiation of 71 without base present. In this case dienols 119 and 123 are formed; however they revert back to 71 and 97

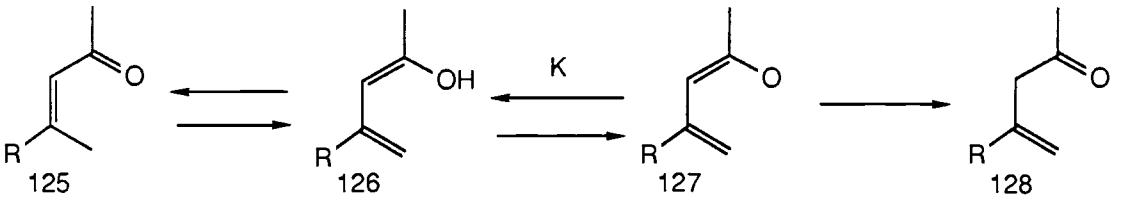
Scheme 33


CO2CH3
71
[T1]
hv
Δ
hv
Δ
hv
Δ
CH3O
OH
121
CH3O
OH
119
OCH3
OH
123
CH3O
OH
121a
CH3O
OH
119a
HO
OCH3
123a
CO2CH3
100
CO2CH3
99
CO2CH3
101

rapidly before deconjugation can proceed. When dienol 121 is formed it relaxes to the more stable s-trans conformation, and thus its lifetime is considerably longer, so that deconjugation can occur, even if only to a minor extent (<5% of reaction mixture).

Weedon et al have recently reported the kinetics of photoenolization and reketonization for ketones 125a,b.[15] They used the technique of laser flash photolysis to directly observe the photodienolate species, 127a,b, and measure their rate of decay by the processes shown in Scheme 34.

Scheme 34

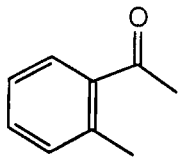


a R = CH3

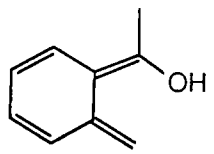
b R = (CH3)3C

Weedon estimated the lifetimes, in water at room temperature, of dienols 126b and 126a to be ca. 0.02 s and (at least) 0.2 s respectively. The different lifetimes are ascribed to 126b preferentially adopting the s-cis conformation to minimize the steric interactions of the -OH and t-butyl group found in the s-trans conformation, thus, placing the molecule into the reactive conformation for the [1,5] shift to regenerate starting material. In 126a, the much smaller methyl group does not have such a large steric demand, and adoption of the s-trans conformation is possible, thus, slowing down the [1,5] shift process by decreasing the amount of material in the reactive s-cis conformation at any one time.

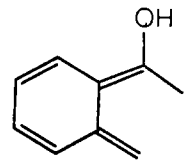
Locking the dienol into a cis conformation, as is the case in the irradiation of o-alkyl aromatic ketone, 129, to form dienol 130 accelerates the rate of reketonization by a factor of approximately 10^6 relative to open chain analogs 125a,b.[13]



129



130



131

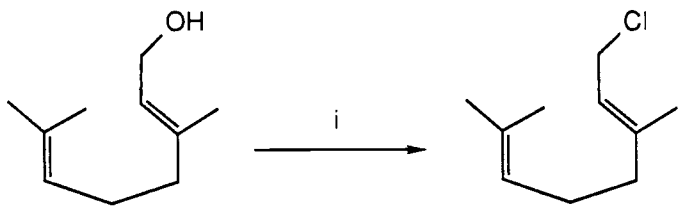
Kinetics studies on the photochemical, base catalysed deconjugation of methyl geranate are fundamentally different from prior studies of this kind.[13,15] With methyl geranate we are using an intramolecular competitive kinetics approach, rather than utilizing sophisticated laser flash photolysis equipment, to get estimates of rates of thermal [1,5] shifts of hydrogen (reketonization of the dienols) relative to the rates of dienol deprotonation. The results from the two approaches parallel each other quite well. This intramolecular competitive kinetics approach for acquiring relative rate information on processes which are difficult to measure directly is still in the preliminary stages of development and should see greater use in the future.

Having developed a good background in the photochemical transformations of the model compound, methyl geranate 71, it was felt that study of the insect juvenile hormone, 74d, was in order. The synthetic route chosen, Scheme 36, revolved around the preparation of methyl (2E,6E)-3,7,11-trimethyl-2,6,10-dodecatrienoate (methyl farnesate), 79d, followed by selective epoxidation of the C-10 - C-11 double bond.[58-59] Weiler et al. have reported the synthesis of 79d with excellent stereocontrol at the trisubstituted double bonds, C-2 and C-6.[60-62]

The synthesis begins with the preparation of geranyl chloride, 132, Scheme 35. The reaction of geraniol, 94 (>99% E isomer) with dimethyl sulfide/N-chlorosuccinimide in CH_2Cl_2 at 0°C yields 132 in 98% yield as a yellow oil, which was used without further purification. The dianion of methyl acetoacetate, formed by successive additions of NaH (1.1 eq, THF, 0°C) and n-BuLi(1.1 eq, THF, 0°C), was alkylated with geranyl chloride (THF, 0°C) to yield

β-ketoester, 133, as an orange oil, which could be purified by reduced pressure distillation. However, examination of the ^{1}H-NMR spectrum showed that the product was pure enough for use in subsequent reactions without further purification. Trapping of the enolate anion of 133, formed by the addition of 1.1 eq of NaH (THF, 0°C), with diethylchlorophosphate gave, stereoselectively, the Z-enolphosphate, 134, in 93% yield.[62] Spectroscopic properties of the synthetic material and authentic sample matched exactly. Coupling of 134 with 3 eq of $LiMe_2Cu$ (Et_2O, -78 — -47°C) yields 79d in 53% yield, after chromatography. Glc analysis of the product showed it to be >95% of the 2E,6E-isomer, 79d, contaminated with 5% of the 2Z,6E-isomer, 79c. Literature[53,62] spectroscopic properties matched exactly those of 79d. Glc retention times of 79d prepared in this reaction and an authentic sample prepared from farnesol, 76d (discussed below) were also identical.

Scheme 35

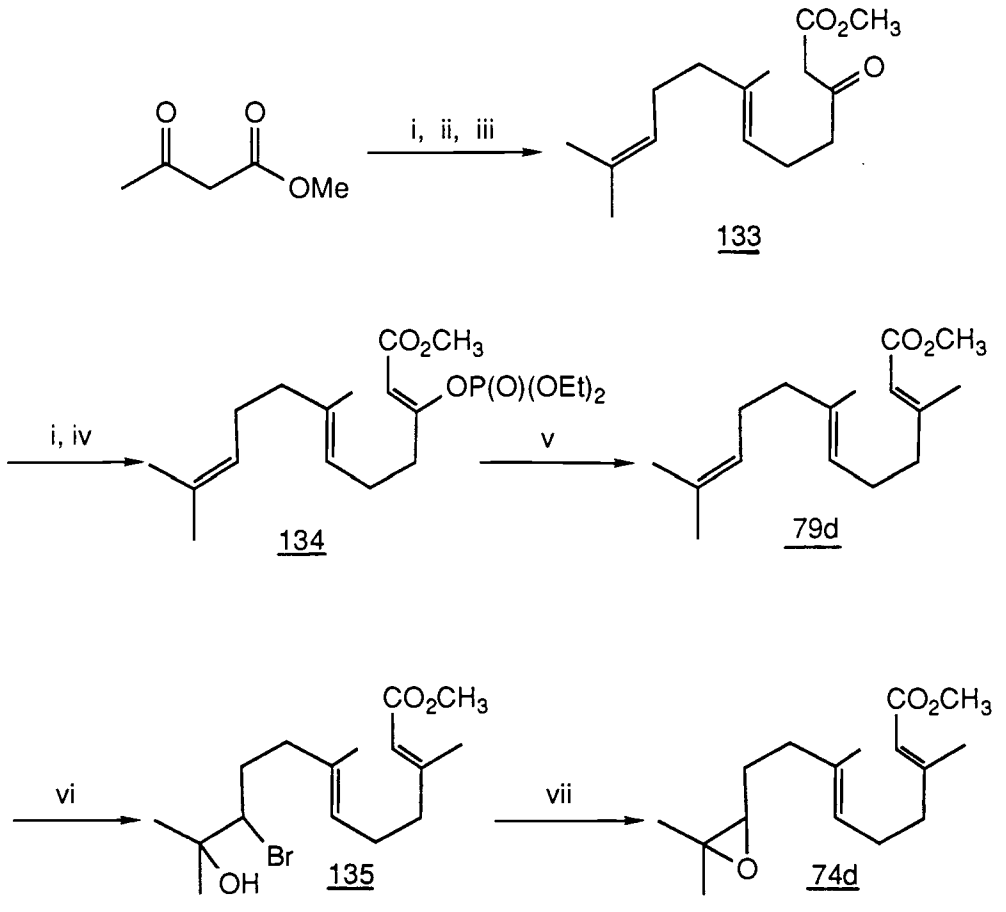


94 132

i, NCS, DMS, CH_2Cl_2, 0°C

Conversion of 79d to the insect juvenile hormone, 74d, was carried out by the regiospecific epoxidation of 79d by modification of the methodology developed by van Tamelen and Curphey.[63] Reaction of N-bromosuccinimide (NBS, 1.05 eq) with 79d in water:glyme (1:1.5) at -20°C afforded bromohydrin, 135, which was taken on in the synthesis without further purification. Epoxide ring closure of 135 with K_2CO_3 (CH_3OH, 25°C) yielded 74d in 23% (this yield is higher when recovered starting material is taken into account). Analysis of the ^{1}H-NMR reveals the expected structural features for a structure consistent with 74: two vinyl protons (5.14 and 5.67 ppm); a 9H multiplet (2.07-2.21 ppm) corresponding to C-3 methyl, C-4, C-5 and

Scheme 36



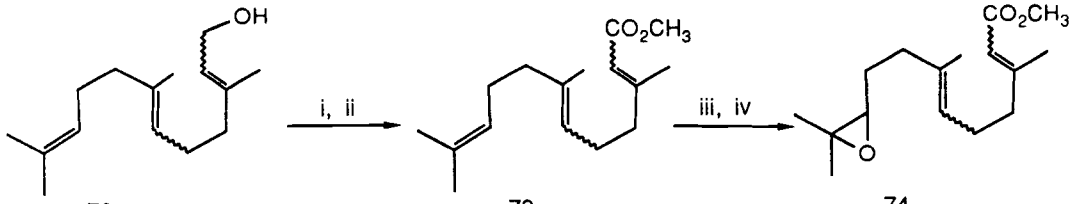
i, NaH, THF, 0°C ii, n-buLi, THF, 0°C iii, 132, iv, $(EtO)_2POCl$, v, $LiMe_2Cu$,

vi, NBS, H_2O/DME, -20°C, vii, K_2CO_3, MeOH

C-9 methylenes; the two methyl groups attached to C-11 (1.26 and 1.30 ppm) have been shifted upfield (they are beta to an epoxide rather than allylic); the methine proton attached to C-10 displays the expected triplet multiplicity and has been shifted downfield to the expected location of a proton attached to an epoxide carbon.[45] The infrared spectrum displays bands at 1220, 870 and 750 cm^{-1}, all consistent with the structure of an epoxide. Comparison of the spectroscopic properties of 74d to those reported in the literature[64-68] show that the assigned structure for 74d is the correct one.

The juvenile hormone was also synthesized, Scheme 37, as a mixture of the four possible E/Z isomers of the two double bonds, 74a (2Z,6Z), 74b (2Z,6E), 74c (2E,6Z) and 74d (2E,6E), using the methodology of Corey et.al.[37,64] Oxidation of farnesol, 79a-d, which comes as a technical mixture of the four isomers, with MnO_2 produced farnesal (four isomers), 136a-d. Proton NMR showed the reaction had gone in >97% yield to the aldehyde. The crude aldehydes were oxidized further to the methyl esters, 79a-d (γ-MnO_2, NaCN, MeOH, HOAc, R.T.). The overall yield from farnesol is 70%, after chromatography. Conversion to the four juvenile hormone isomers, 74a-d, was readily accomplished by epoxidation of the C-10 double bond using the procedure just described for the 2E,6E isomer, 74d.

Scheme 37



76	79	74
a = 2Z, 6Z	a = 2Z, 6Z	a = 2Z, 6Z
b = 2Z, 6E	b = 2Z, 6E	b = 2Z, 6E
c = 2E, 6Z	c = 2E, 6Z	c = 2E, 6Z
d = 2E, 6E	d = 2E, 6E	d = 2E, 6E

i, MnO_2, HEXANE, 0 C, ii, MnO_2, NaCN, HOAc, MeOH, RT iii, NBS, H_2O/DME, iv, K_2CO_3, MeOH

Glc analysis of the isomer mixtures at each stage of the synthesis proved to be very helpful in the identification of the configuration about the C-2 and C-6 double bonds. Table 4 summarizes the results of these analyses. The gas chromatograph of the farnesol mixture showed only three peaks in the ratio of 1:5.4:4.3, the middle peak (relative area 5.4) was assumed to be a mixture of 76b,c. The gas chromatogram of the methyl farnesate mixture displays the expected four peaks in the ratio of 1:1.05:3.03:2.8. The Juvenile hormone mixture also shows the expected four peaks in the ratio of 1:1.61:2.67:3.34. Katzenellenbogen and Savu,[53] in studies on the ç-alkylation of senecioic acid anions with alkyl halides, generated the mixture of four methyl farnesates, 79a-d, and determined from detailed analyses of their ^{1}H-NMR spectra that the order of elution from a 3% OV-17 glc column is 79a (2Z,6Z), 79b (2Z,6E), 79c (2E,6Z) and 79d (2E,6E) (our analyses were done on an 8% OV-17 column). This result fits in with the general observation that this author has made, that the retention time (order of elution), on a non-polar or moderately polar glc column for non-polar or moderately polar compounds, increases by sequentially changing the double bonds from the Z to the E configuration.[56] Presumably, a more linear molecule can interact to a greater degree (stronger adsorption to the liquid stationary phase) and thus be retained longer in the column. Examination of table 4 reveals the following: the 2Z,6Z isomer is always the smallest component and elutes first, and the 2E,6E isomer is the last peak to elute (this was tested by coinjection of authentic samples of 79d and 74d). In the course of the synthesis of the juvenile hormone, 74a-d, no reaction was carried out that has been shown to isomerize the double bonds (see prior discussions of methyl geranate, 71, and the synthesis of 74d). Since the areas under the peaks for the four isomers are significantly different, reversal of elution order would be immediately obvious. To validate the statement above one must assume that the four isomers of 79 all undergo bromohydrin formation at the same rate and to the same extent. This may not be a completely valid argument since the procedure relies on a coiling of the molecule in the polar solvent (glyme:water) and the ability of the molecule to

coil is a function of the stereochemistry about the double bonds. It is evident that the first and fourth peaks (74a and 74d respectively) do not change their elution order. However the case for 74b and 74c is not so clearcut. A more detailed structure analysis of this mixture is in order for the future. The glc retention time for 74d synthesized by the Weiler chemistry and the fourth of four peaks to elute from the isomeric mixture of juvenile hormones were found to be identical based on coinjection in the gc.

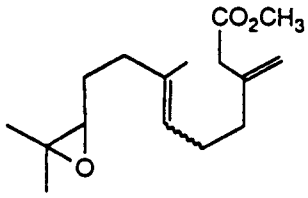
Table 4. Glc Data for 76, 79 and 74[a].

Compound	2Z,6Z	2Z,6E	2E,6Z	2E,6E
76	1.0	(5.4)[b] ----	-----	4.3
79	1.0	(4.1)[b] 1.05	3.03	2.8
74	1.0	(4.3)[b] 1.6	2.67	3.34

a) Areas are relative to the first peak to elute and are measured relative to dodecane as an internal standard.
b) Sum of the areas for 2Z,6E and 2E,6Z peaks.

In a series of exploratory experiments, 74d was irradiated with 254 nm lamps as a 0.1 M solution in ether with various additives. First, in ether alone without any additives, a glc analysis of the product mixture provided evidence for similar chemical transformations of 74d and 71. About a dozen new product components were shown to form in the irradiation of 74d in ether, with four major peaks (>90% of the photolysis mixture) and several minor products, which were for the most part two unresolved peaks each (a major peak with a minor product shoulder). Collection of pure samples proved beyond the current separation ability of the glc columns in use and will require extensive work in the future. Preliminary analysis of ^{1}H-NMR spectra for some of the minor components reveal features compatible with structures analogous to 72 and 73 but the spectra are of mixtures and of very small quantities of impure material, so no positive

identifications can be made at this time. In a second irradiation, with 0.5 equivalents of 1,2-DMI (to determine which products arise from photodeconjugation), five new peaks as major products with distinctly different retention times in the gas chromatogram, relative to the major products of direct irradiation, were formed. Looking at the structure of 74d one would predict six possible deconjugation products, 150-155. However at this time these have not been isolated and fully characterized. The third irradiation was carried out in the presence of propiophenone (to determine which products arise from the triplet state) and resulted in the distinct enhancement of yields for the minor products (those formed in <2% having a lower retention time in the glc) of the direct irradiation.



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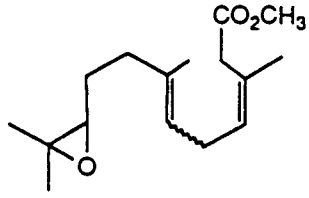

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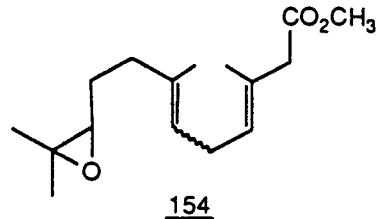

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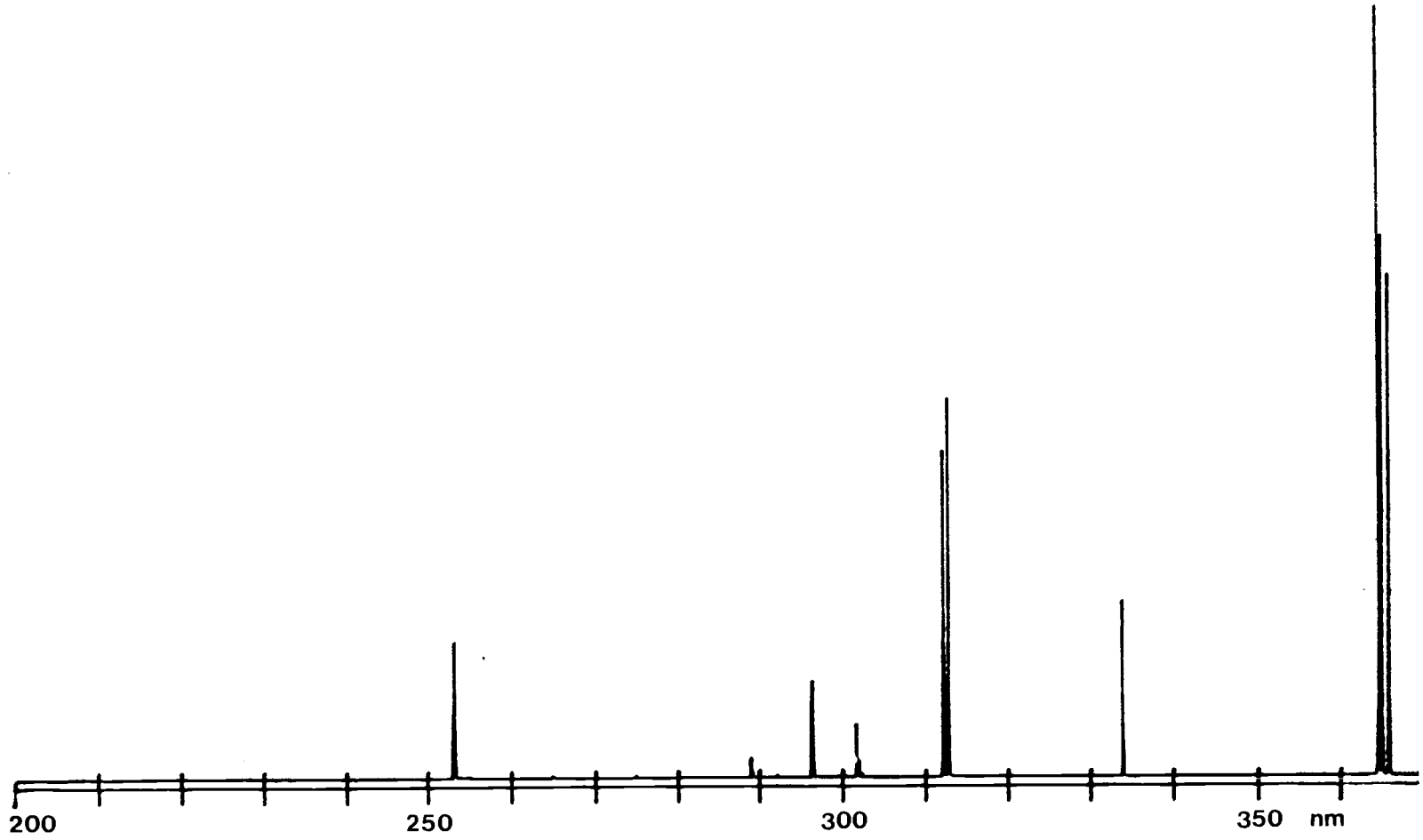
155

The unexpected result to come out of these preliminary irradiation experiments was the rapid E/Z isomerization of the C-6 double bond. These peaks were identified by coinjection of the photolysis mixture with the synthetic mixture of 74a-d and the major products of the photolysis proved to have identical retention times. A GC-MS of the photolysis mixture also showed that the products formed in greater than 2% to be isomers of the starting material (M^+ at m/e 266) It was initially thought (in a naive way) that the C-6 bond would not be isomerized to any appreciable extent since the UV absorption of a trisubstituted double bond is zero above about 210 nm. The 254 nm lamps used in the irradiations was ruled out as a source of radiation in the 200 nm range by measuring their output spectrum on a Spex 1402 spectrophotometer with an RCA 31034 photomultiplier tube. It is not possible to draw quantitative conclusions about the relative intensities of the various emission lines in the spectrum because the sensitivity of the photomultiplier tube drops off as one approaches

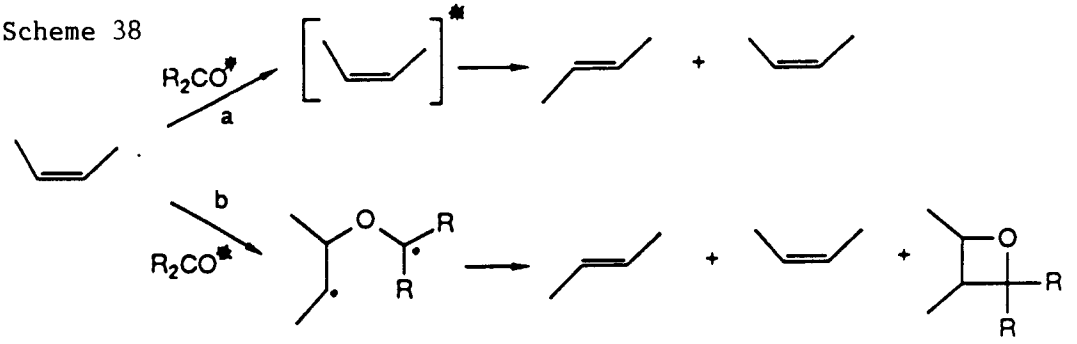
Figure 19. UV Output Spectrum of Rayonet 254 nm lamps.



200 nm (no response below about 200 nm). The results are shown in Figure 19. It can be seen from this lamp output spectrum that there is no UV output below 254 nm.

A reasonable answer to the question of E/Z isomerization of the isolated C-6 double bond in 74d can be drawn by analogy with the photochemical E/Z isomerization of simple olefins by triplet sensitizers such as acetone, benzene, acetophenone etc.[69,66] It was noted that the composition of the photostationary state in irradiations of olefins with triplet sensitizers varied as a function of the triplet energy of the sensitizer. Two competing mechanisms were proposed to account for this fact, Scheme 38. First, if the triplet energy of the sensitizer is close to that of the olefin (the triplet energy of ethylene is around 80-82 Kcal/mol, benzene is at 84 kcal/mol and acetone at 80 kcal/mol) then energy is transferred by direct collisional interaction. Second, if the triplet energy of the sensitizer is very low relative to the olefin (benzophenone, 68 kcal/mol), then a collision complex, originally thought to be a 1,4-diradical (Schenk diradical) 137, is formed in which isomerization is competitive with fragmentation of the complex. For the Schenk diradical pathway, if the diradical is sufficiently stable so that intersystem crossing is competitive with complex fragmentation then oxetanes, 138, are expected to be a side product and indeed this is the case for species with a very low triplet energy (benzophenone). With triplet sensitizers of intermediate energy (acetophenone 72 Kcal/mol) there is a competition between the two processes. The existence of two intermediates was shown conclusively by Salteil et al in the photoisomerization of cis or trans 2-pentene.[71] Two decay ratios for the isomerization were obtained depending on whether acetone or benzophenone were used as sensitizer. Interaction of the carbonyl group with the alkene was also shown by Wagner and Kochevar who measured the rate of carbonyl triplet quenching by olefins.[72] Isobutylene was found to quench the triplet of butyrophenone with a rate of 49×10^7 mol^{-1} s^{-1}.

Scheme 38

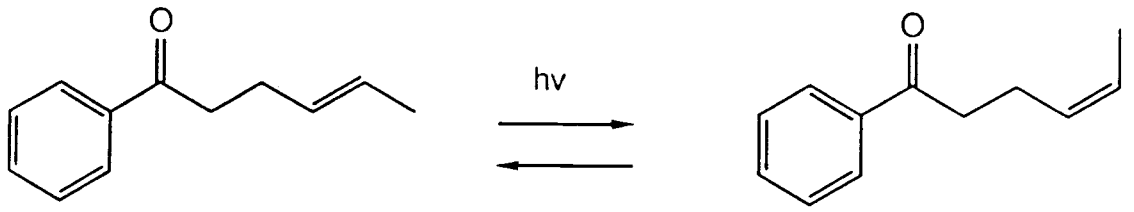


137 138

By 1975 it was a well established belief that the intermediate responsible for isomerization of olefins, by low triplet energy sensitizers, was indeed a charge transfer exciplex rather than a diradical species,[72,73] and an intramolecular study of the rate of quenching for 1-phenyl-4-hexen-2-one, 139, was reported by Morrison and Tisdale.[74] The values of intramolecular and intermolecular quenching of aryl ketones is summarized in Table 5. The point to note is that the intramolecular process is about 300 times faster than the intermolecular process and the value of intermolecular quenching is very close to that reported by Wagner (above). Examination of the structure of 139 and comparing it to that of 71 shows the relative locations of the two functional groups to be about the same, so it is reasonable to expect facile formation of an intramolecular complex in irradiations of 71.

To probe the question of the existence and nature of an intermediate complex in the isomerization of 74d, two new analogs of methyl geranate were synthesized, methyl (2E,6E)-3,7-dimethyl--2,6-nonadienoate, 92d, and methyl 3,7-dimethyl-2-octenoate (both the E and Z isomers), 93a,b. The synthesis of these two compounds is described below.

Synthesis of methyl (2E,6E)-3,7-dimethyl-2,6-nonadienoate,92d, was accomplished as shown in Scheme 39, using the chemistry developed by van Tamelen and McCormick.[58] Geraniol, 94, was protected as the trityl ether, 140, by treatment with triphenylmethyl chloride in pyridine (50°C, 18 hr), followed by selective epoxidation of the C-6 double bond with m-chloroperoxybenzoic acid (MCPBA, 1.0 eq,



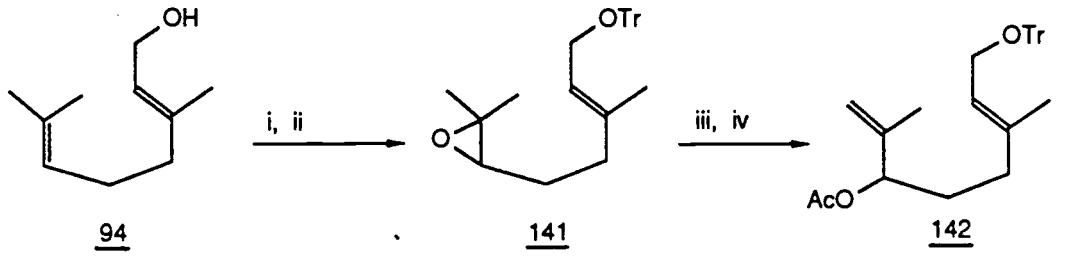
139

Table 5. Some Rate Constants for Quenching the Triplet Benzoyl Group by Double Bonds.[74]

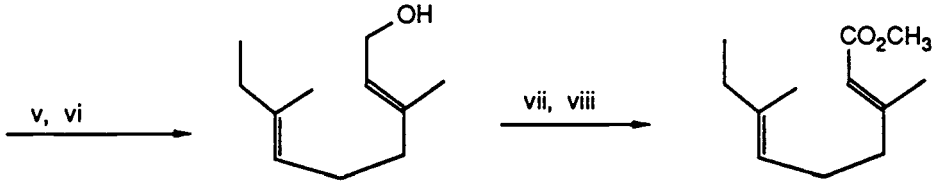
Intramolecular		Intermolecular	
Compound	k_{ct}, 10^9 mol^{-1} sec^{-1}	olefin	k_{ct}, 10^7 mol^{-1}, sec^{-1}
139a	15.0	cis-2-pentene	5.0
139	15.0	trans-2-pentene	2.0
		1-pentene	0.8

CH_2Cl_2, -20°C) afforded trityl ether epoxide , 141, as a very viscous yellow oil in 95% yield. The regiochemistry of the epoxidation was assigned by the complete loss of the C-6 vinyl signal at 5.44 ppm in the ^{1}H-NMR. As expected, 141 was smoothly converted to the isomeric allylic alcohol, 145 by heating the epoxide with LDA (lithium diisopropyamide, 5.0 eq) in ether, at reflux for 2 h. The yield of this isomerization reaction, after chromatography, was 95%, and the spectroscopic properties were consistent with the structure, 145. The ^{1}H-NMR displayed three vinyl peaks (4.85, 4.96 and 5.48 ppm) and a 1H triplet at 4.05 ppm, corresponding to the proton on C-6 which has been shifted downfield, as expected, from 2.99 ppm in the epoxide. The IR spectrum displays the strong broad OH absorption at 3400 cm^{-1}. Conversion of 145 to the corresponding allylic acetate, 142, was accomplished in 88% yield, after chromatography by the standard method (Ac_2O, 4-N,N-dimethylamino pyridine (DMAP), pyridine, 18 h, 25°C). The spectroscopic properties were all in accord with the structure 142. The OH bands disappeared in the IR spectrum. The mass spectrum displayed the M^+ peak at m/e 454; M - 243 and M - 259, which result from the two possible fragmentations of the ether bond. The ^{1}H-NMR displayed the expected acetate methyl singlet at 2.06 ppm and a downfield shift of the methine (relative to the allylic alcohol 145) attached to the carbon bearing the acetate group. The ^{13}C-NMR displayed a carbonyl signal at 170 ppm for the acetate group. Displacement of the acetate group in an S_n2'like reaction was accomplished by the method of Henrick et al.[75,76] Addition of 142 to a stirred solution of $LiMe_2Cu$, in ether at -20°C, resulted in clean conversion to 146. The crude 146 was not purified further and taken on directly to the homologated geraniol, 143, by methanolysis of the trityl ether protecting group (6% HCl/methanol, 25°C, 2 h) in 48% yield for the two reactions, after chromatography.[77] Glc analysis of the alcohol, 143, revealed two products in a 95:5 ratio. The major product was assumed to be the expected (2E,6E)-isomer of 143 and the minor product was assumed to be the (2E,6Z)-isomer of 143. The remaining two steps in the synthesis employ the method of Corey et al.[37] Oxidation of the allylic

Scheme 39



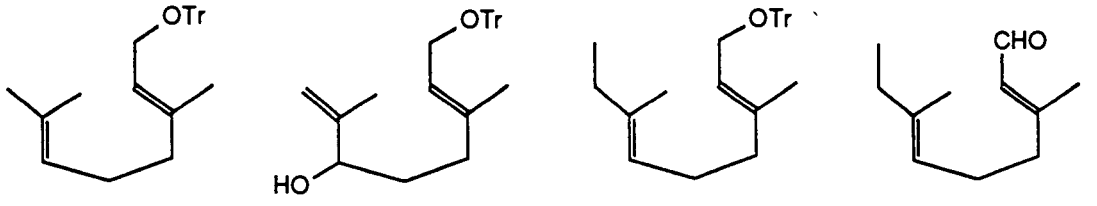
94 141 142



143 92d

i, TrCl, py ii, MCPBA, -20 C; iii. LDA, Et_2O, reflux; iv. AC_2O, py, DMAP

v. $LiMe_2Cu$; vi. 6% HCl/MeOH; vii, MnO_2, HEXANE, 0 C; vii, MnO_2, MeOH, NaCN, HOAc



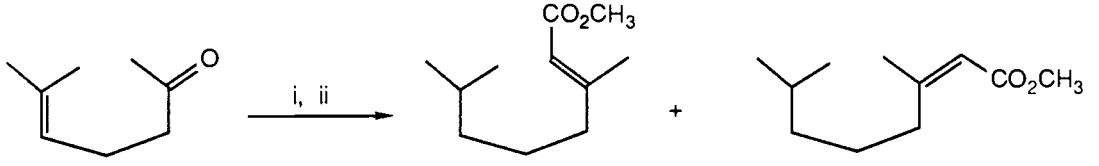
144 145 146 147

alcohol, 143, by MnO_2 in hexane afforded the aldehyde, 147, in 98% yield and this material was taken on without further purification. Reaction of 147 with MnO_2, NaCN and HOAc in methanol yielded methyl (2E,6E)-3,7-dimethyl-2,6-nonadienoate, 92d, 33% after chromatography. Glc analysis of the product showed it to be a 95:5 mixture of two compounds, which were shown to be isomeric by MS (M^+ m/e = 196 for both). The major compound was subsequently shown to be the (2E,6E)-isomer,92d, and the minor product the (2E,6Z)-isomer,92c. The spectroscopic properties of 92d are consistent with the structure proposed. The IR spectrum displays absorptions at 1720, 1650 and 850 cm^{-1}, all indicative of an α,β-unsaturatred ester containing a trisubstituted double bond. The IR spectra of 71 and 92d are amazingly similar. The ^{1}H-NMR spectra of 92d and 71 are also superimposable aside from the shift of the methyl singlet at 1.69 ppm in 71 to 0.97 ppm as part of an ethyl, A_3X_2 spin system. The methylene quartet is found at 1.97 ppm (the expected value for an allylic set of methylene protons). The remainder of the proton NMR spectrum shows remarkably little (none!) splitting of the peaks, a characteristic of the E configuration of the C-2 double bond.

Synthesis of methyl (2E)-3,7-dimethyl-2-octenoate, 93b, was accomplished in two steps as shown in Scheme 40. Hydrogenation of 6-methyl-5-hepten-2-one (an ant alarm pheromone), 148, followed by a Horner-Emmons reaction of the saturated ketone, 149, with trimethylphosphonoacetate (MeOH, NaOMe, 25°C) afforded a mixture of 93a and 93b in a 71:29 ratio, 51% overall yield.[78] The two isomers were readily separated by silica gel chromatography (95:5, hexane:ether). The two isomers had very similar spectroscopic properties but the ^{1}H-NMR provided excellent structural information. In 93b the 3H singlet corresponding to the allylic methyl group on C-3 is located at 2.17 ppm and the allylic methylene protons are a triplet at 2.11 ppm. In going to 93a the allylic methyl is shifted upfield to 1.86 ppm and the allylic methylene protons are shifted downfield to 2.61 ppm. These shifts in going from the E to Z isomers can be explained by the deshielding effect of the carbomethoxy

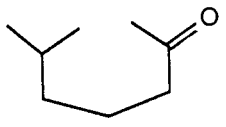
group. In 93b the allylic methyl protons are deshielded, and shifted downfield, relative to the allylic methyl protons in 93a by being cis to the carbomethoxy group. Conversely in 93a the allylic methylene protons are deshielded, and shifted downfield, relative to the allylic methylene protons in 93b by being cis to the carbomethoxy group.

Scheme 40



148 93b 93a

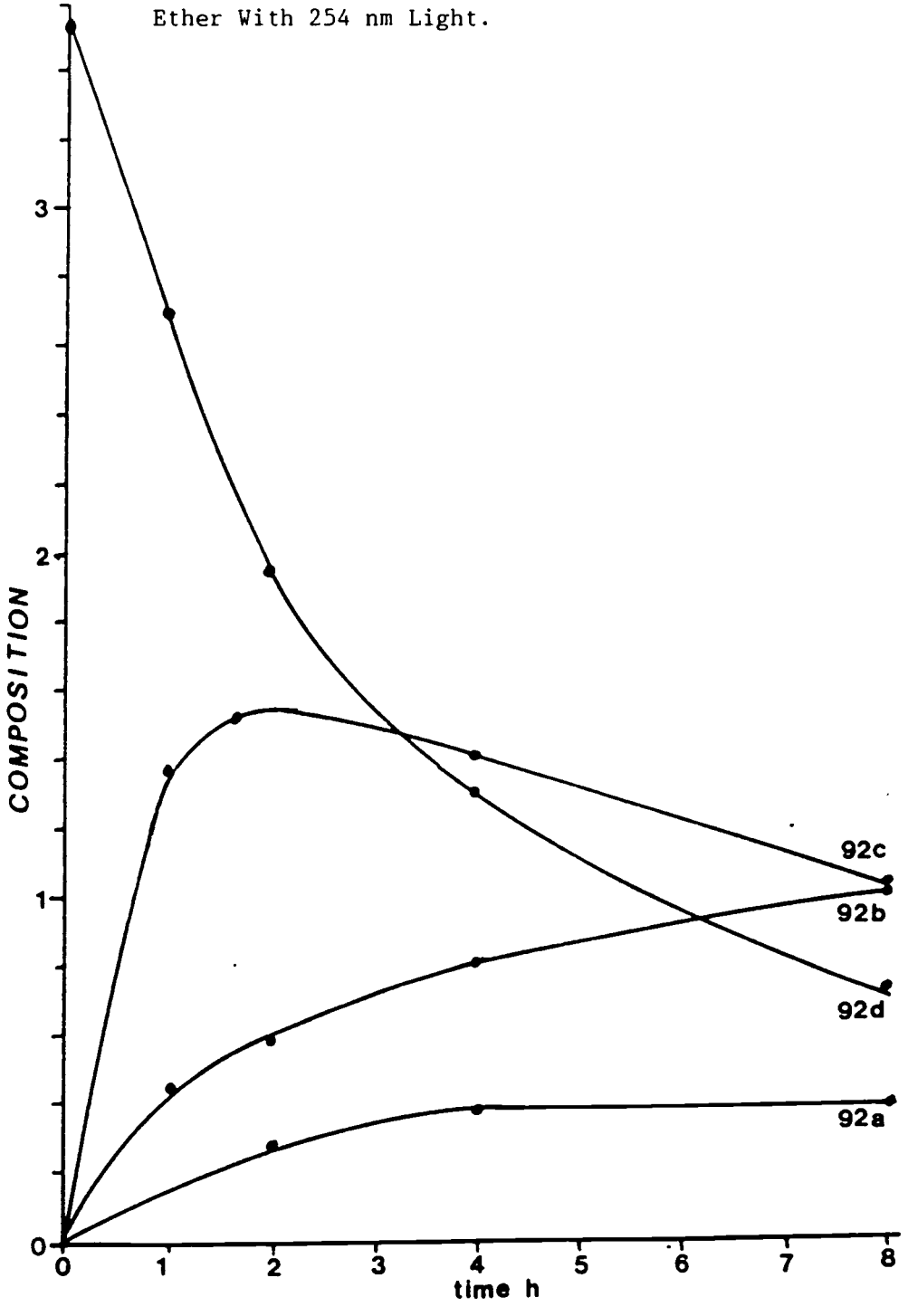
i, H_2, Pd/C; ii, $(MeO)_2P(O)CH_2CH_3$, NaOMe, MeOH



149

Prior to any studies designed to probe the nature of the intermediate responsible for the E/Z isomerization and its charge transfer properties a 0.1 M solution of 92d was irradiated for 8 h with samples removed at intervals and analysed for relative composition of E/Z isomerization about the two double bonds. The results of this are presented in figure 20 and it can be seen that the C-6 double bond does undergo isomerization but with a lower relative quantum yield than the corresponding C-2 double bond. The next phase was to probe the charge transfer nature of the intermediate reponsible for the isomerization of the C-6 double bond and to this end 0.01 M solutions of 71 and 93b, were irradiated for 6 min in solvents of varying polarity. It was reasoned that if the exciplex involved a charge separated species then irradiation of 71 in solvents of increasing polarity should increase the relative quantum yield of E/Z isomerization, and similarly irradiation of 93b in the same solvents should leave the relative quantum yield for E/Z isomerization

Figure 20. Irradiation Time vs Relative Composition[a] of Double Bond Isomerization Products for Irradiation of 92b in Ether With 254 nm Light.



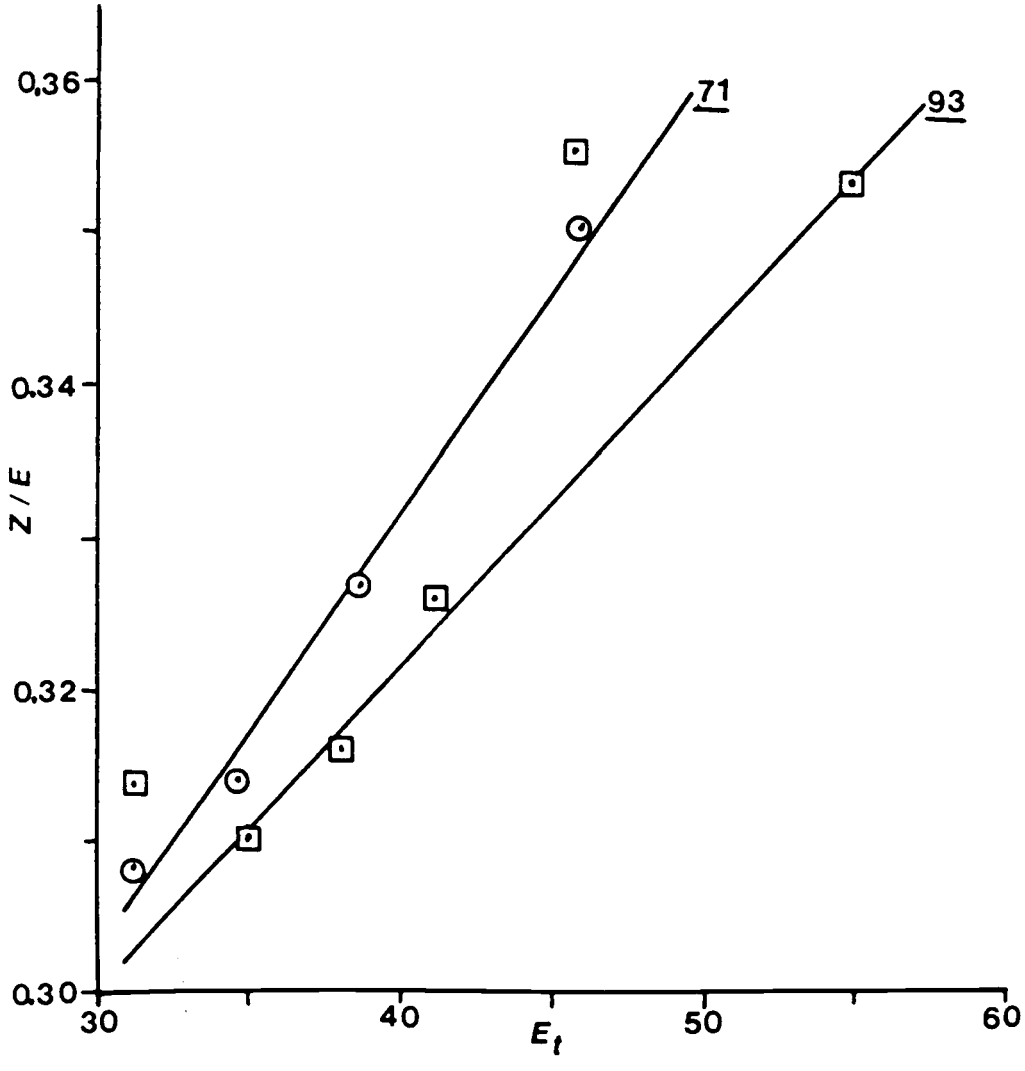
a. Composition is relative to internal standard, (dodecane).

unchanged (for the ideal case). This is shown in Figure 21, plotting the ratio of Z/E product vs E_t[79]. The solvent parameter E_t is is similar to the dielectric constant but takes into account the fact that when a molecule is excited by light the electronic redistribution of the molecule is very rapid relative to reorganization of the solvent shell or nuclear relaxation (the Franck-Condon principle) and solvation of the excited species is not optimum.

For 93b it was expected that formation of an intermolecular exciplex would be minimized at the concentration used (0.01 M). However, examination of Figure 21 clearly shows an enhancement of the quantum yield for the E/Z isomerization process with increasing solvent polarity (E_t). This indicates that indeed there is a charge transfer exciplex involved in the isomerization, but at the concentration used it must be an intermolecular exciplex rather than an intramolecular one as hoped for. The line for 71 also has a positive slope with increasing solvent polarity, but with the limited results of these exploratory experiments it is not possible to establish the inter- or intramolecular nature of this exciplex.

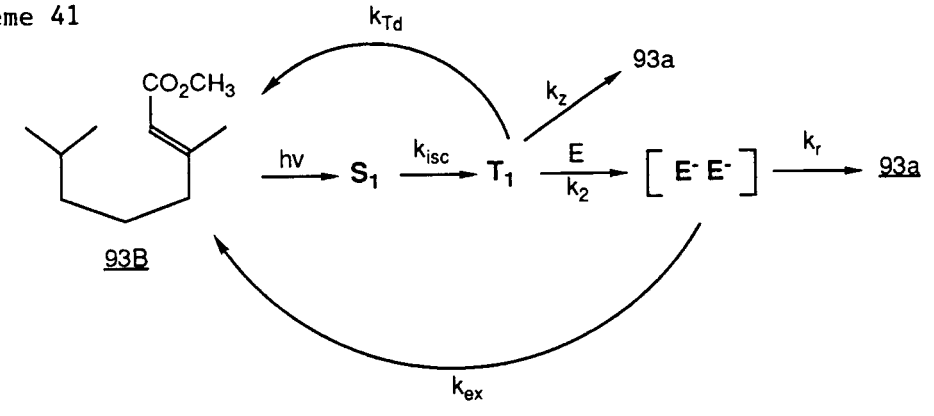
The question of intramolecular exiplex formation in 71 can be addressed by irradiation of 71 in solvents of varying polarity, in a concentration range that is known to be below the limits for intermolecular exciplex formation. This limit can be found by irradiation of 93b (and 71) in solutions of increasing dilution and plotting the inverse of the relative quantum yield for the isomerization process versus the inverse of the ester concentration. An analysis of the kinetics of isomerization, including formation of an intermolecular exciplex, 156, was carried out for 93b. The results of the kinetics analysis, based on scheme 41, are summarized below. Assuming that the extent of reaction for formation of products other than E/Z isomerization is low, then a kinetic expression based on the quantum yield for isomerization can be derived. Equation 12 shows that there is an expected straight line correlation of (relative quantum yield)$^{-1}$ vs [93b]$^{-1}$, a Stern-Volmer plot, for the case where $k_2[E] >> k_z$. Going back to a series of irradiations carried out in ether at increasing dilution for 1h (for 71, 93b and 92d), the

Figure 21. Z/E Composition Ratios of 71 and 93b vs E_t.



results of the Stern-Volmer plot are shown in Figures 22-24. The point to note is that the quantum yeild does increase with increasing concentration of the esters (71, 93b and 92d), indicating that there is formation of an intermolecular exciplex. It would be expected that at the lower concentrations (0.002-0.0008 M) this line should flatten out to have zero slope in the case of 93b, Figure 22, but this does not happen. For the very limited data available it is clear that in the concentration range studied, the intermolecular exciplex of 93b is the significant contributor to the isomerization process. The same behavior just described is also evident in Figures 23 and 24. The kinetics of exciplex formation of 71 or 92d are complicated by the additional processes that have already been descibed in Scheme 29, and for Equation 12 to be valid the extent of reaction must be very low (i.e. little if any formation of products other than E/Z isomerization). Figure 25 shows that for an irradiation time of 1h this criterion is not met and so Figures 23 and 24 must be interpreted with caution. The trend does suggest however, the formation of an exciplex and indicates that these experiments must be redone with much shorter irradiation times and a wider variation of concentrations. This work is currently in progress in our laboratories and should yield interesting insights to the problem of E/Z isomerization in the juvenile hormone.

Scheme 41



$$1/O = \frac{k_2[E] + k_{Td}}{k_2[E]F} = 1/F + \frac{k_{Td}}{k_2 F [E]} \qquad (11)$$

$$\text{where } F = \frac{k_r}{k_r + k_{ex}}$$

Figure 22. Quantum Yield Dependence of 93a from 93b vs [conc.]$^{-1}$

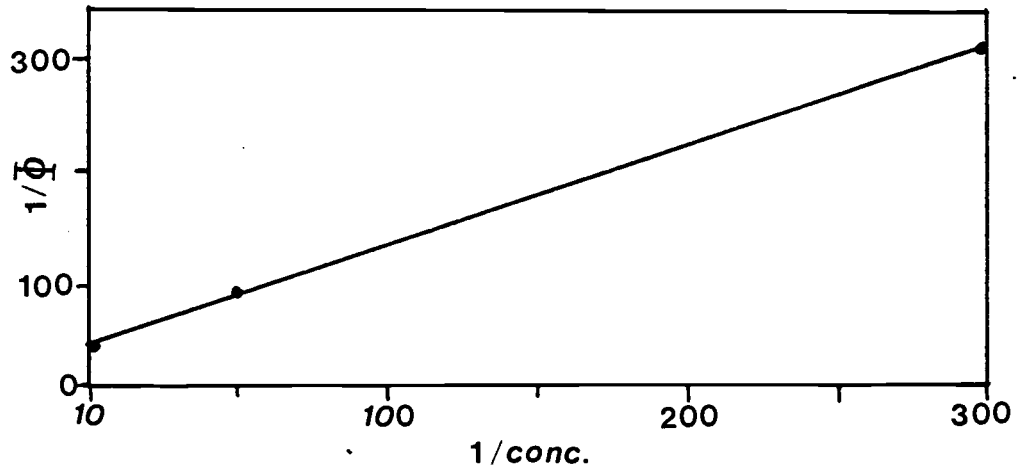


Figure 23. Quantum Yield Dependence of 92c from 92d vs [conc.]$^{-1}$

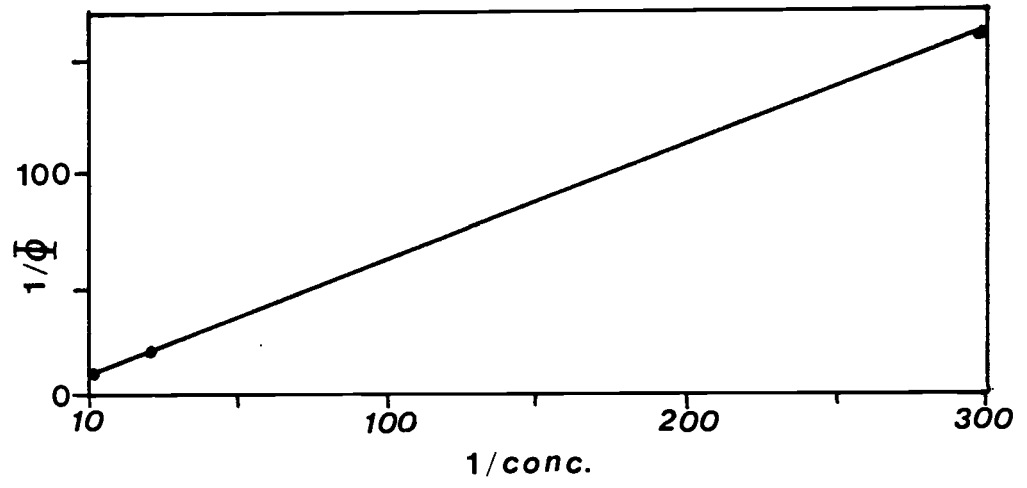


Figure 24. Quantum Yield Dependence of 97 from 71 vs [conc.]$^{-1}$

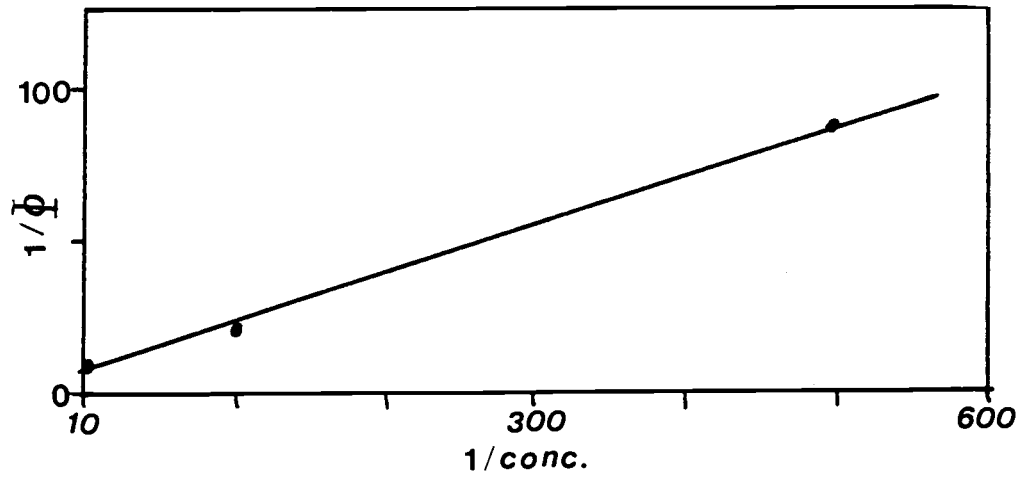
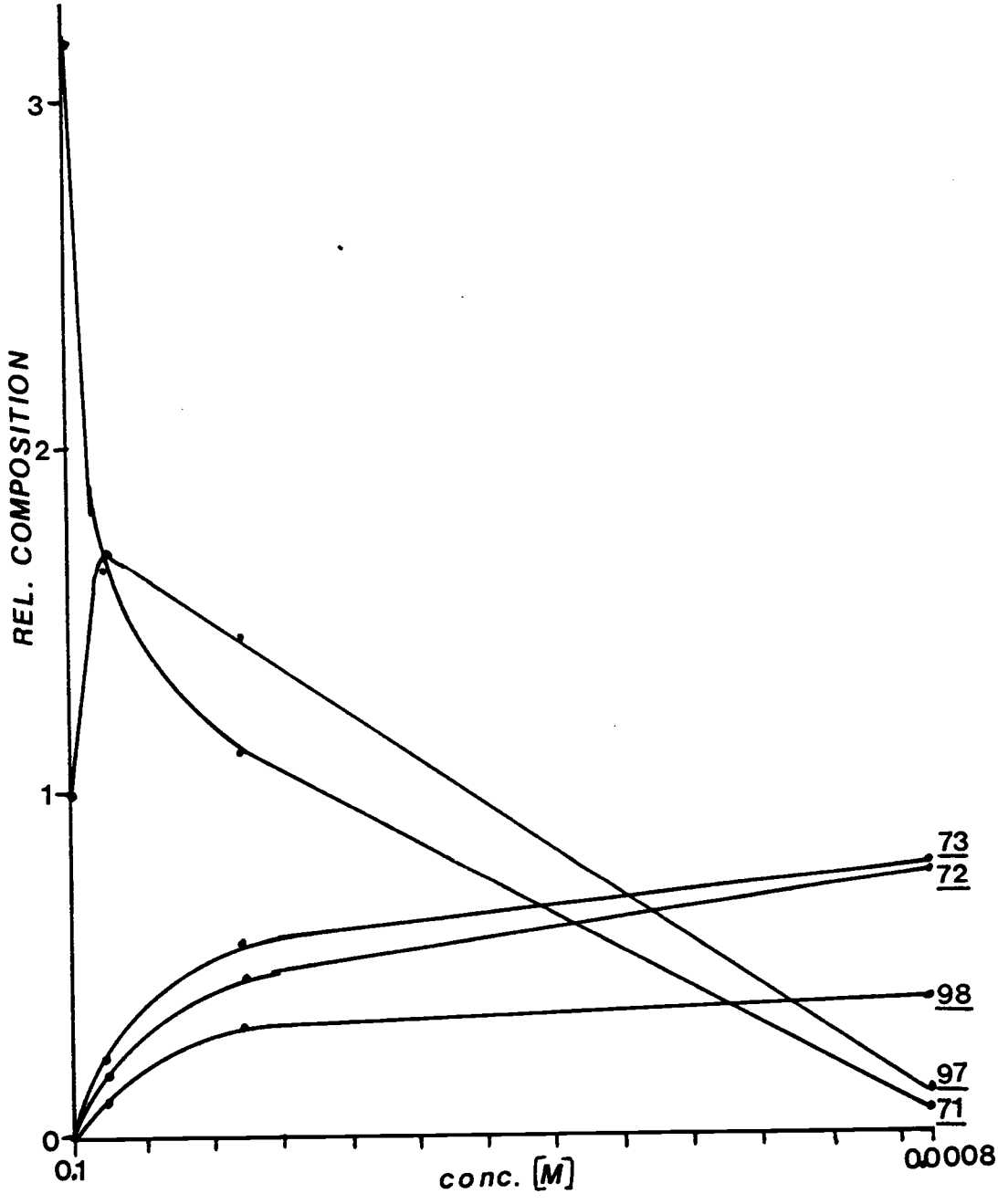


Figure 25. Relative Composition of Photolysis Components in the Irradiation of 71 as a Function of Dilution.



Conclusions. It can be seen from the discussions above that several important things have been learned about the photochemistry of insect juvenile hormone analogs and á,â-unsaturated esters in general during the course of this research. Irradiation of methyl geranate leads to the formation of seven product components. The product 98 has not previously been reported in the literature arising from any related photochemical system. The kinetics of base catalysed photodeconjugation have been elucidated and found to be valid, even though the complexity of the methyl geranate reaction manifold would seem to make this an impossible task. The approach of using intramolecular competitive reaction kinetics to obtain valuable information on photodeconjugation processes in á,â-unsaturaated esters is reported here for the first time. Previous work has relied on laser flash photolysis experiments to obtain information similar to that reported here. An exciplex has been shown to exist in the photolysis of methyl geranate, 71, 92d and 93b. However, the inter- or intramolecular nature of the exciplex is still under investigation. There is preliminary evidence that 74d undergoes analogous photoprocesses to 71, and 92d such as the rapid E/Z photoisomerization of the C-6 double bond. Since isomerization of the double bonds at C-2 and C-6 significantly decreases the biological activity of these compounds the photochemistry of these compounds takes on greater environmental significance.

EXPERIMENTAL

General Procedures. Nuclear magnetic resonance spectra (NMR) were recorded on either a Bruker AM-400 (^1H at 400.14 MHz, ^{13}C at 100.62 MHz) or Varian FT-80 (^1H at 79.54 MHz, ^{13}C at 20.00 MHz) in $CDCl_3$ with tetramethylsilane as an internal standard. Infrared spectra (IR) were obtained with a Perkin-Elmer Model 735B spectrophotometer with the 1601 cm^{-1} band of a polystyrene film as reference or a Mattson Sirius 100 spectrometer. Ultraviolet spectra were obtained using a Cary 210 spectrometer. Gas chromatographic analyses were carried out using a Varian 3700 gas chromatograph equipped with a flame ionization detector and Hewlett-Packard 3373B integrator using one of the following columns: (A),10% OV-17, 20 ft; (B),7% OV-17, 20 ft; (C),3% OV-17, 20 ft. All columns were packed in 0.125 inch copper tubing using Chromasorb-W, AW, DMCS, 60/80 mesh. Preparative gas chromatography was carried out on a Hewlett-Packard, F and M scientific 700 gas chromatograph equipped with a thermal conductivity detector using one of the following columns:(D), 10% OV-17, 20 ft; (E),15% OV-17, 20 ft. Both columns were packed in 0.25 inch copper tubing with Chromasorb-W, AW, DMCS, 60/80 mesh. Mass spectra were obtained on a Finnigan 4023 mass spectrometer equipped with a Finnigan 9610 gas chromatograph. Exact mass determinations were performed on a Kratos MS-50 mass spectrometer.

All solvents were used as received from the manufacturer except as noted. Diethyl ether and tetrahydrofuran were both distilled off sodium/benzophenone ketyl immediately prior to use. Cyclohexane, 1,2-dimethoxyethane (DME) and methylene chloride were fractionally distilled from calcium hydride onto 3 Å molecular sieves. Tert-butanol was fractionally distilled from barium oxide onto 3 Å molecular sieves. Methanol was predried over sodium sulfate followed by careful fractional distillation onto 3 Å molecular sieves.

All photolysis samples were placed in Ace Glass Co. 170x15 mm quartz, sealable sample tubes (catalog no. 7415-30) and degassed with

three freeze/thaw cycles in liquid nitrogen on a vacuum line evacuated with a mercury diffusion pump unless otherwise noted. All articles of glassware used in making up samples for photolyses (quartz tubes, volumetric flasks, etc.) were rinsed with 10% aqueous HCl, distilled water and acetone prior to being oven dried. The light source for all photolyses, unless otherwise noted, was a Rayonet Type RS, preparative photochemical reactor (Southern New England Ultraviolet Co.) equipped with eight 253.7 nm lamps and an eighteen sample tube merry-go-round device.

Two-dimensional NMR experiments. All two-dimensional spectra of 73, 100 and 101 were recorded at 297 K with a Bruker AM-400 spectrometer equipped with an Aspect 3000 computer operating in Fourier transform mode with quadrature detection. Standard Bruker pulse programs were used unless otherwise noted.

Two-dimensional ^{1}H - ^{1}H shift correlated (COSY-45) were aquired with the following parameters. For all samples a sinebell resolution enhancement was performed prior to Fourier transformation and other parameters are listed below for each sample:
for 73 there were 1024 data points in the f2 and f1 domains, sweep width of 1923 Hz, 256 experiments (8 scans each) with an incremental delay of 0.4 ms; for 100 there were 1024 datapoints in the f2 and f1 domains, sweep width of 2809 Hz, 256 experiments (8 scans each) with an incremental delay of 0.356 ms; for 101 there were 1024 data points in the f2 and f1 domains, sweep width of 2427 Hz, 256 experiments (8 scans each) with an incremental delay of 0.412 ms.

Two-dimensional heteronuclear ^{1}H - ^{13}C shift correlated (HETCOR) experiments were aquired with the following parameters. For 73 there were 256 and 2000 data points in f1 and f2 respectively, sweep widths were 2300 Hz and 14286 Hz in f1 and f2 respectively, 128 experiments (32 scans each) with an incremental delay of 0.217 ms. Gaussian-Lorentz resolution enhancenment (Gaussian factor of 0.8) with resolution enchancement in f2 of -13 Hz and -8 Hz in f1 prior to Fourier transform. For 100 there were 512 and 2000 data points in f1 and f2 respectively, sweep widths were 1400 Hz and 12500 Hz in f1 and

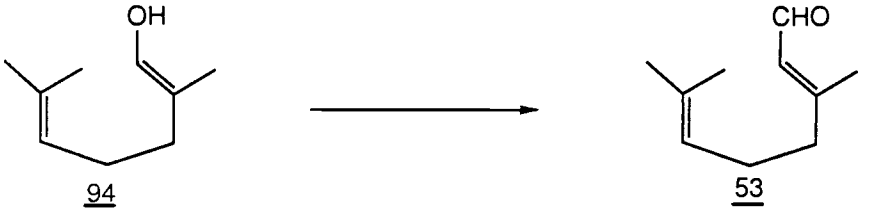
f2 respectively, 256 experiments (144 scans each) with an incremental delay of 0.179 ms. Gaussian-Lorentz resolution enhancement (Gaussian factor of 0.8) with resolution enhancement of -5 Hz and -12 Hz in f1 and f2 respectively, prior to Fourier transform. For 101 there were 512 and 2000 data points in f1 and f2 respectively, sweep widths were 1250 and 13158 Hz in f1 and f2 respectively, 256 experiments (144 scans each) with an incremental delay of 0.200 ms. Gaussian-Lorentz resolution enhancenment (Gaussian factor of 0.8) with resolution enhancement in f2 of -6 Hz and -4 Hz in f1 prior to Fourier transform

A two-dimensional ^{1}H J-Resolved (JRES) spectrum was obtained for 73 with the following parameters. There were 2000 and 512 data points in f1 and f2 respectively, sweep width was 69.44 and 2222.22 Hz in f1 and f2 respectively, 256 experiments (32 scans each). Sinebell in f2 and Gaussian-Lorentz (Gaussian factor of 0.9) in f1 and resolution enhancement in f1 of -0.2 Hz prior to Fourier transformation. Tilt and symmetrization functions wer performed on the transformed spectrum.

A. Synthesis.

Preparation of activated Manganese dioxide. A 5% solution of aqueous potassium permanganate (79 g in 1.5 L) at 60 °C was added in three portions over 5 minutes to a stirred 5% solution of aqueous manganese sulfate (113 g in 1.5 L) also at 60 °C. The resulting brown suspension was stirred for an additional hour at 60 °C. The fine brown precipitate was collected on a fritted glass filter and washed with 4 L of distilled water to ensure removal of excess salts of potassium and manganese. The precipitate was oven dried at 60 °C to yield 120 g of a brown amorphous powder which was ground to a fine powder in a mortar and pestle prior to use.

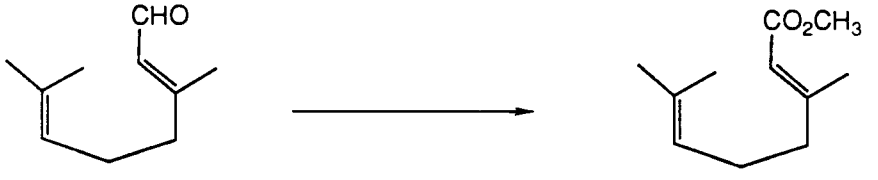
(2E)-3,7-Dimethyl-2,6-octadienal (53)(citral.[37]



94 53

To a 1 L round bottom flask containing a stirred suspension of 25 g of activated manganese dioxide in 300 mL of hexane at 0 °C was added 5 g of geraniol (32.5 mmol, Aldrich Gold Label). The brown suspension was stirred at 0 °C for 30 min. After removal of the manganese dioxide by filtration it was washed with 300 mL of ether and all solvents were removed in vacuo to yield 4.5 g (91%) of citral. The citral was shown to be >98% pure by glc (column B) and was used without further purification: ^{1}H-NMR δ 1.61 (3H, s), 1.70 (3H, s), 2.22 (7H, m), 5.08 (1H, br s), 5.89 (1H, d J = 8 Hz) and 10.0 (1H, d J = 8 Hz); IR (film) 2960 (s, sh), 2930 (s), 2860 (s, sh), 1675 (s), 1635 (m, sh), 1450 (s), 1380 (m), 1200 (s), 1125 (s) and 850 (m) cm^{-1}; MS m/e 152 (M^+), 94, 84, 69 and 41 (100).

Methyl (2E)-3,7-dimethyl-2,6-octadienoate (71)(methyl geranate).[37]



53 71

Dry methanol (300 mL) was placed into a 1 L round-bottomed flask and cooled to 0 °C. To this flask was slowly added, with vigorous stirring, 25 g of activated manganese dioxide. To this suspension was added citral, 53, (5.00 g, 32.9 mmol), sodium cyanide (6.00 g, 122 mmol) and 1 mL of glacial acetic acid. The mixture was stirred at room temperature for 24 hrs at which time 7 mL of saturated sodium bicarbonate was added to neutralize any excess hydrogen cyanide. The

manganese dioxide was removed by filtration and washed with 600 mL of ether. The combined organic portions were concentrated in vacuo to an orange slurry. The crude product was extracted from 300 mL of water with ether (3x200 mL) and the combined extracts were washed with water and brine. After drying over $MgSO_4$, the solvent was removed in vacuo to give 4.2 g of crude 71 as an orange oil. The crude product was purified via silica gel chromatography (85:15, hexane:ethyl acetate)to yield 3.0 g (50%) of methyl geranate, 71, as a pale yellow oil:^{1}H NMR (80 MHz) δ 1.60 (3H, s), 1.69 (3H, s), 2.16 (7H, s), 3.69 (3H, s), 5.07 (1H, br s) and 5.67 (1H, s); ^{13}C NMR (20 MHz) δ 17.67, 18.71, 25.70, 26.36, 41.13, 50.54, 115.59, 123.39, 132.37, 159.76 and 166.94; IR (film) 2970 (s, br), 1720 (s), 1650 (m), 1430 (m), 1220 (s), 1140 (s) and 1050 (w) cm^{-1}; MS m/e 182 (M^+), 123, 114 and 69 (100);UV (methanol) ε_{254} = 1900.

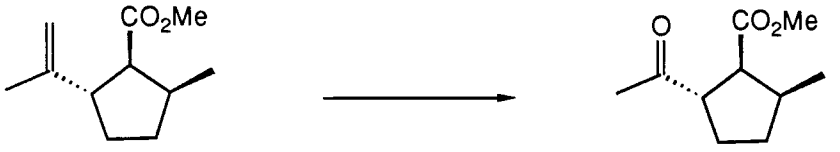
Ozonolysis of methyl 5-methyl-2-isopropenyl-4-hexenoate (98).

98 102

Ozone was bubbled through a solution of 17 mg of 98 in 5 mL of methylene chloride in a 10 mL flask which contained a magnetic stir bar. The addition was carried out at -78 °C until a blue color persisted. The solution was stirred an additional 15 min at -78 °C at which time nitrogen was bubbled through the system to remove excess ozone. Solvent was removed in vacuo and the residue was dissolved in 5 mL of acetone. After cooling the flask to 0 °C, excess Jones reagent ($KCrO_3$, H_2SO_4, acetone) was added and the solution was stirred for 15 min at 0 °C. The mixture was filtered through celite, the solid washed with hot acetone, and the acetone was removed in vacuo. The crude product was dissolved in 5 mL of ether and cooled to 0 °C. Excess diazomethane was added to the solution and the solution was stirred at 0 °C for 15 min. Solvent was removed in vacuo and the crude

product was purified by preparative glc (column D) to yield 2 mg of ketodiester (102): ^{1}H NMR (80 MHz) δ 2.36 (3H, s), 2.90 (1H, d J = 7.5 Hz), 2.95 (1H, d J = 7.5 Hz), 3.67 (3H, s), 3.77 (3H, s) and 4.01 (1H, t J = 7.5 Hz), High Resolution MS m/e calcd for $C_8H_{12}O_5$ 188.068, found 188.068 ± 0.010.

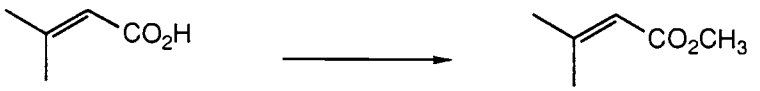
Ozonolysis of methyl 2-isopropenyl-5-methylcyclopentanoate (73).



73

Ozone was bubbled through a solution of 10 mg of the 73 in 5 mL methylene chloride contained in a 10 mL flask equipped with a magnetic stir bar. The reaction temperature was maintained at -78 °C and the addition continued until a blue color persisted. The solution was stirred an additional 15 min at -78 °C at which time nitrogen was bubbled through the system to remove excess ozone. Solvent was removed in vacuo and the residue was dissolved in 5 mL of acetone. After cooling the flask to 0 °C, excess Jones reagent ($KCrO_3$, H_2SO_4, acetone) was added and the solution was stirred for 15 min at 0 °C. The mixture was filtered through celite and the solid was washed with hot acetone. Acetone was removed in vacuo. The crude product was dissolved in 5 mL of ether and cooled to 0 °C. Excess diazomethane was added to the solution and the solution was stirred at 0 °C for 15 min. Solvent was removed in vacuo and the crude product was purified by preparative glc (column D) to yield 4 mg of ketoester .^{1}H NMR (360 MHz) δ 1.48 (1H, m), 1.66 (1H, m), 1.90 (1H, m), 2.20 (3H, s), 2.45 (1H, m), 3.22 (1H, t J = 8.1 Hz), 3.42 (1H, q J = 8.6 Hz) and 3.71 (3H, s); High Resolution MS m/e calcd for $C_{10}H_{16}O_3$ 188.068, found 188.068 ± 0.010.

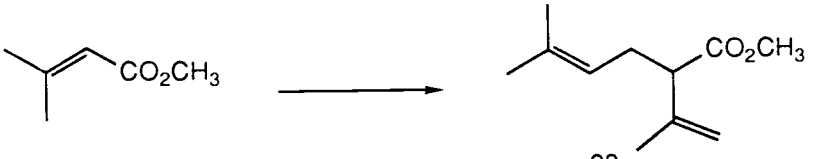
Methyl 3-methyl-2-butenoate (103), (methyl senecioate)



103

A dry 100 mL, three-necked flask fitted with a condenser surmounted by a drying tube of calcium chloride, pressure equalizing addition funnel and magnetic stir bar was charged with thionyl chloride (12.4 mL, 0.17 mol) and warmed to 55 °C. Senecioic acid (10 g, 0.10 mol) dissolved in 20 mL dry THF was added dropwise to the flask through the addition funnel. After addition was complete the reaction was heated at reflux for 20 min at which time excess thionyl chloride and THF was removed by short path distillation. Methanol (8.5 mL, 0.24 mol) was added dropwise to the acid chloride at room temperature and the solution was stirred an additional 30 min. At this time the crude ester was poured into 50 mL of brine and extracted twice with ether. The combined ether portions were washed twice with saturated $NaHCO_3$ and once with brine. Solvent was removed, after drying with $MgSO_4$, in vacuo. The crude ester was distilled through a short path column at reduced pressure to yield 6.8 g (60%) of methyl senecioate (103): ^1H NMR (400 MHz) δ 1.90 (3H, s), 2.18 (3H, s), 3.68 (3H, s) and 5.68 (1H, s); ^{13}C (100 MHz) δ 20.08, 27.28, 50.65, 115.61, 156.61 and 167.04; IR (film) 2950 (m), 1720 (s), 1660 (s), 1440 (m), 1235 (s), 1150 (s), 1050 (m) and 860 (m) cm^{-1}; MS (m/e) 114 (M^+),100, 91, 83 (100) and 55.

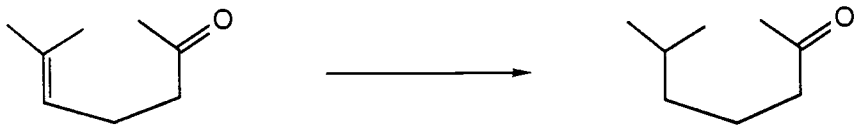
Methyl 2-isopropenyl-5-methyl-4-hexenoate (98).



103 98

The method of Katzenellenbogen was used with no modifications[K-2]. A dry 50 mL single necked round-bottomed flask charged with diisopropyl amine (0.107 g, 1.05 mmol), a magnetic stir bar and 20 mL of dry THF was cooled under an argon atmosphere to -78 °C. n-Butyl lithium (0.42 mL, 2.5 M, 1.05 mmol) was added dropwise via dry syringe and the solution was stirred for 5 min. To the lithium diisopropylamide (LDA) solution at -78 °C was added, dropwise, 103 (0.100 g, 0.877 mmol) in 3 mL dry THF. The reaction was warmed to room temperature and stirred under an argon atmosphere for 2 hr. At this time prenyl bromide (0.391 g, 2.63 mmol, Aldrich) in 1 mL dry THF was added and the solution was stirred an additional 1.5 hr under an argon atmosphere. The reaction was quenched by the addition of 25 mL of water. The aqueous phase was separated and extracted twice with ether. The combined organic extracts were washed once with 10% HCL and twice with brine and the solvent was removed in vacuo after drying over $MgSO_4$. The crude product was passed through a short plug of silica gel (90:10 hexane:ether) and after removal of solvent in vacuo 0.141 g (88%) of the title compound, (98), was isolated and was shown by glc to be 95% of the desired α-alkylated and 5% of the γ-alkylated material (methyl geranate). 50 mg of 98 was isolated for spectroscopic characterization via preparative glc (column A): ^{1}H NMR (400 MHz) δ 1.60 (3H, s), 1.65 (3H, s), 1.72 (3H, s), 2.24 (1H, p J = 7.3 Hz), 2.48 (1H, p J = 7.3 Hz), 3.01 (1H, t J = 7.6 Hz), 4.86 (1H, s), 4.87 (1H, m) and 4.99 (1H, tt J = 7.0, 1.0 Hz); ^{13}C NMR (100 MHz) δ 17.79, 20.39, 25.74, 28.93, 51.78, 53.20, 113.64, 121.05, 131.53, 142.39 and 173.95; IR (film) 2920 (m), 1730 (s), 1650 (w) and 1160 (m) cm^{-1}; MS (m/e) 182 (M^+), 139, 123, 122, 114, 107, 83, 82, 81, 69 (100) and 53 .

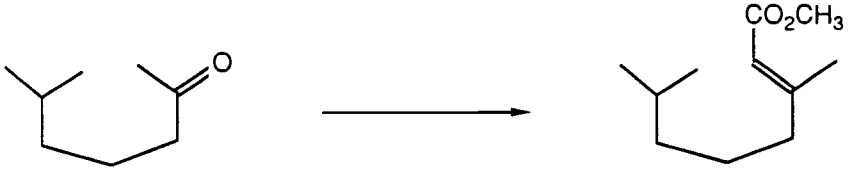
6-Methyl-2-heptanone (149).



148 149

A 125 mL pressure bottle fitted with a hydrogen gas inlet was charged with 6-methyl-5-hepten-2-one (10.0 g, 79.2 mmol, Aldrich) in 25 mL of 95% ethanol and Pd (10%) on carbon (0.5 g). The flask was purged of air by repeated filling with hydrogen (35 psig) and venting to the atmosphere. After five purge cycles the flask was filled with 35 psig hydrogen and placed on a Parr shaker for 4 hr. The catalyst was removed by filtration through celite which was washed with copious amounts of 95% ethanol. Ethanol was removed in vacuo to yield 6 g (60%) of the title ketone (149). ^{1}H NMR (400 MHz) δ 0.87 (6H, d J = 7.5 Hz), 1.17 (2H, m), 1.54 (3H, m), 2.14 (3H, s) and 2.41 (2H, t J = 7.5 Hz); ^{13}C NMR (100 MHz) δ 21.68, 22.43, 27.81, 29.82, 38.36, 44.00 and 209.38; IR (film) 2950 (s), 1715 (s), 1475 (m), 1380 (s), 1370 (s),1180 (s) and 1060 (w) cm^{-1}; MS (m/e) 182 (M^{+}), 167, 151, 139, 123, 114, 107, 93, 83, 69 (100), 55 and 41.

Methyl 3,7-dimethyl-2-octenoate (92).

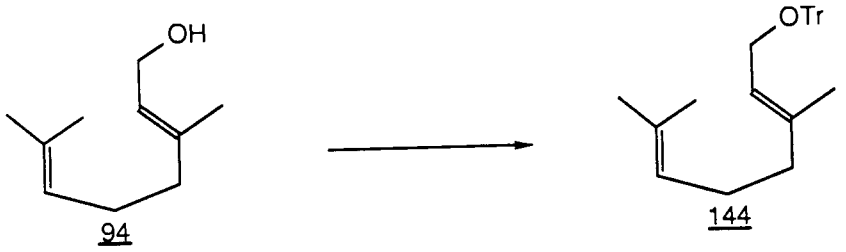


149 93b

A 1 L, three-necked, round-bottomed flask fitted with a magnetic stir bar, two 125 mL pressure equalizing addition funnels and a nitrogen inlet was charged with a solution of trimethylphosphonoacetate (4.55 g, 25.0 mmol, Aldrich) in 250 ml of dry ether. One of the addition funnels was charged with 100 mL of a 0.52 M solution of sodium methoxide in methanol (Na, 1.2g, 52 mmol, dissolved in 100 mL dry

methanol). The other addition funnel was charged with a solution of 6-methyl-2-heptanone (2.85 g, 22.2 mmol) in 100 mL of dry ether. The two solutions were added dropwise at the same rate over a period of 20 min to the flask containing the trimethylphosphonoacetate. The resulting solution was stirred an additional 30 min at room temperature. The reaction was quenched by the addition of 300 mL of water. The aqueous layer was extracted with ether (3x100 mL) and the combined organic portions were washed with water (2x100 mL). After drying with $MgSO_4$, the solvent was removed in vacuo leaving 2.1 g (51%) of the crude ester as a 29:71 mixture of Z:E isomers. Separation of the E and Z isomers was accomplished by Silica gel chromatography (95:5, hexane:ether). After removal of solvent in vacuo 0.91 g (22.5%) of the E isomer, 92b, and 0.35 g (8.6%) Z isomer,92a, were isolated: 92b, exhibited the following spectral properties: ^{1}H NMR (400 MHz) δ 0.88 (6H, d J = 7.5 Hz), 1.17 (2H, m), 1.50 (3H, m), 2.12 (2H, t J = 7.5 Hz), 2.25 (3H, s), 3.69 (3H, s) and 5.66 (1H, s); ^{13}C NMR (100 MHz) δ 18.65, 22.47, 25.13, 27.79, 38.36, 41.10, 50.67, 114.97, 160.66 and 167.23; IR (film) 2950 (s), 1720 (s), 1655 (s), 1450 (s), 1380 (m), 1370 (m), 1235 (s), 1160 (s) and 1050 (m) cm^{-1}; MS (m/e) 184 (M^+), 153, 152, 127, 114 (100),110, 95, 82 and 69; UV (methanol) $\varepsilon_{254} \approx 1000$.
92a, exhibited the following spectral properties: ^{1}H NMR (400 MHz) δ 0.87 (6H, d J = 6.6 Hz), 1.22 (2H, m), 1.46 (2H, m), 1.55 (1H, p J = 6.6 Hz), 1.88 (3H, s), 2.60 (2H, t J = 7.8 Hz), 3.67 (3H, s) and 5.65 (1H, s); ^{13}C NMR (100 MHz) δ 22.54, 25.12, 25.95, 27.81, 33.48, 38.88, 50.71, 115.50, 161.20 and 166.77; IR (film) 2950 (s), 1720 (s), 1445 (m), 1380 (m), 1370 (m), 1235 (s), 1195 (s) and 1050 (w) cm^{-1}; MS (m/e) 184 (M^+), 153, 152, 127 (100), 114, 95, 82, 69 and 55; UV (methanol) $\varepsilon_{254} \approx 700$.

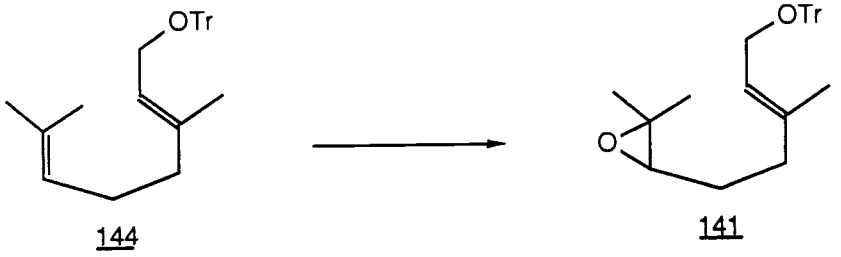
(2E)-3,7-Dimethyl-1-triphenylmethoxy-2,6-octadiene (144).



94 144

A 250 mL single-necked, round-bottomed flask fitted with a magnetic stir bar was charged with geraniol, 94, (10.0 g, 64.9 mmol, Aldrich), trityl chloride (18.1 g, 64.9 mmol) and 100 mL dry pyridine. The solution was warmed to 50 °C and stirred for 24 h. The crude product was diluted with 300 ml of diethyl ether and washed repeatedly with 10% aqueous HCl to remove the pyridine. The ether solution was then washed with saturated $NaHCO_3$ and brine. Solvent was removed in vacuo, after drying with $MgSO_4$, to yield 24.4 g (95%) of 144 as a very viscous, yellow oil which was used without further purification: ^1H NMR (400 MHz) δ 1.46 (3H, s), 1.61 (3H, s), 1.69 (3H, s), 2.04 (2H, m), 2.08 (2H, m) 3.59 (2H, d, J = 6.5 Hz), 5.11 (1H, br t J = 5.5 Hz), 5.44 (1H, br t J = 6.5 Hz) and 7.20-7.48 (15H, m); ^{13}C NMR (100 MHz) δ 16.52, 17.71, 25.70, 26.41, 39.57, 61.28, 86.58, 121.31, 124.07, 126.80, 127.72, 128.69, 131.54, 138.48 and 144.39; IR (film) 3060 (w), 3025 (w), 2925 (s), 1600 (w), 1490 (m), 1450 (s), 1060 (s) and 715 (s) cm^{-1}; MS (m/e) no detectable M^+ peak (388), 243 (100), 165, 105 and 69.

(2E)-6,7-Epoxy-3,7-dimethyl-1-triphenylmethoxy-2-octene (141)

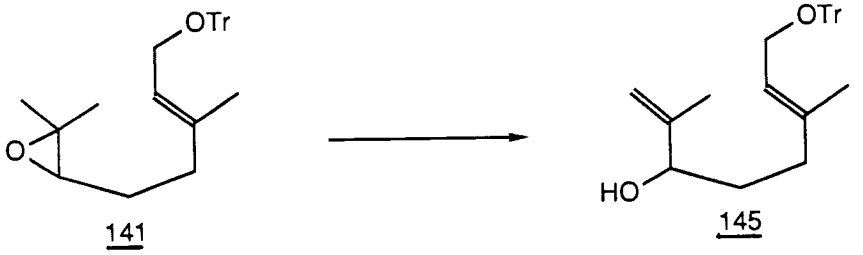


144 141

A 1 L, three-necked, round-bottomed flask fitted with a mechanical stirrer and a 500 mL addition funnel, was charged with

dienetrityl ether, 144, (24.4 g, 61.6 mmol) and 500 ml of methylene chloride and was cooled to -20 °C (dry ice/ carbon tetrachloride). The addition funnel was charged with technical (85%) 3-chloroperoxybenzoic acid (13.0 g, 60.0 mmol, Aldrich) dissolved in 300 mL of methylene chloride. The contents of the addition funnel were added dropwise over a period of 30 min. The solution was stirred an additional 3 h at -20 °C. At this time, 500 mL of a 10% Na_2SO_3 was added to destroy any remaining peroxides. The aqueous layer was separated and extracted once with methylene chloride. The combined organic layers were washed twice with brine and dried over $MgSO_4$ prior to removal of solvent in vacuo to yield 25.4 g (100%) of 141 as a very viscous, yellow oil: ^{1}H NMR (400 MHz) δ 1.27 (3H, s), 1.31 (3H, s), 1.48 (3H, s), 1.63 (2H, m), 2.16 (2H, m), 2.72 (1H, t J = 6.3 Hz), 3.61 (2H, d J = 6.3 Hz), 5.47 (1H, br t J = 6.3 Hz) and 7.20 - 7.47 (15H, m); ^{13}C NMR (100 MHz) δ 16.51, 18.74, 24.86, 27.16, 36.15, 58.35, 61.14, 64.03, 86.61, 121.94, 126.83, 127.72, 128.65, 137.53 and 144.29; IR (film) 3060 (m), 3030 (m), 2960 (s), 2930 (s), 1600 (w), 1495 (s), 1455 (s), 1050 (s) and 715 (s) cm^{-1}; MS (m/e) 412 (M^+), 261, 260, 228, 215, 181, 169, 153, 106, 85 (100) and 59 (100).

(2E)-3,7-Dimethyl-1-triphenylmethoxy-2,7-octadien-6-ol (145).

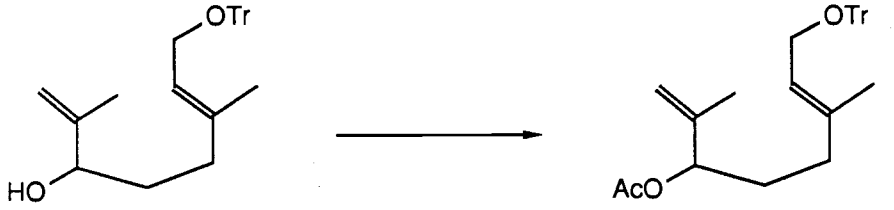


141 145

A dry, 1 L three-necked, round-bottomed flask fitted with a mechanical stirrer, reflux condenser, pressure equalizing addition funnel and nitrogen inlet was charged with diisopropyl amine (34.8 mL, 247 mmol) and 300 mL of dry ether. This solution was cooled to 0 °C and purged with dry nitrogen. To the addition funnel was added, using a cannula for transfer, n-butyllithium (98.8 mL, 247 mmol, 2.5 M). The butyllithium solution was added dropwise over 5 min to the flask

and the resulting solution was stirred an additional 5 min at 0 °C. Epoxide 141 (25.4 g, 61.6 mmol) dissolved in 100 ml of ether was placed into the addition funnel and added dropwise over a 5 min period to the LDA solution. After stirring at 0 °C for 5 min the solution was heated at reflux for 2 h. The reaction was cooled to 0 °C and quenched with saturated NH_4Cl. The aqueous phase was separated and extracted twice with ether. The combined ether portions were washed with saturated $NaHCO_3$, until the ether layer was neutral to litmus, followed by brine. The solvent was removed, after drying with $MgSO_4$, in vacuo to yield a viscous yellow oil. The crude product was purified by silica gel chromatography. Hexane:ether (90:10) was used to elute off all products with a higher R_f than the desired alcohol, which remained at the baseline, followed by elution with hexane:ethyl acetate (75:25). After removal of solvent in vacuo 24.2g (95.3%) of the allylic alcohol 145 was isolated as a colorless, viscous oil. ^1H NMR (400 MHz) δ 1.48 (3H, s), 1.60 (1H, br s), 1.67 (2H, m), 1.74 (3H, s), 2.06 (2H, m), 3.60 (2H, d J = 6.4 Hz), 4.06 (1H, t J = 6.4 Hz), 4.85 (1H, d J = 1.4 Hz), 4.95 (1H, d J = 1.7 Hz), 5.48 (1H, t J = 6.3 Hz) and 7.20-7.50 (15H, m); ^{13}C NMR δ 16.54, 17.60, 32.89, 35.50, 61.20, 75.56, 86.62, 111.11, 121.70, 126.83, 127.72, 128.68, 138.22, 144.35 and 147.41; IR (film) 3600-3200 (s, br), 3060 (m), 3030 (m), 2940 (s), 2860 (s, sh), 1600, (w), 1490 (m), 1450 (s), 900 (s) and 770 (m) cm^{-1}.

(2E)-6-Acetoxy-3,7-dimethyl-1-triphenylmethoxy-2,7-octadiene (142).

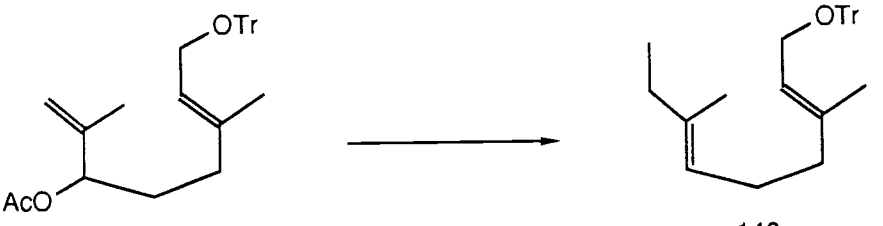


145 142

To a 500 mL single-necked, round-bottomed flask was added a magnetic stir bar, 200 mL of dry pyridine, allylic alcohol, 145, (24.2 g, 58.7 mmol), 100 mL of acetic anhydride and 4-N,N-dimethylaminopyridine (DMAP) (0.10 g, 0.82 mmol (cat.)). The resulting solution was stirred

for 18 h at room temperature at which time it was cooled to 0 °C and 100 mL of methanol was added to destroy the unreacted acetic anhydride. The crude reaction mixture was diluted with 500 mL ether and washed repeatedly with 10% aqueous HCl to remove the pyridine. The combined aqueous portions were extracted twice with ether then the combined organic portions were washed twice with saturated $NaHCO_3$ followed by brine. After drying the organic layer with $MgSO_4$ solvent was removed in vacuo to yield 23.5 g (88.2%) of 145 as a viscous, orange oil: ^1H NMR (400 MHz) δ 1.46 (3H, s), 1.70 - 1.79 (5H, m (includes 3H, s), 1.99 (2H, q J = 6.6 Hz), 2.06 (3H, s), 3.60 (2H, d J = 6.3 Hz), 4.90 (1H, s, br), 4.95 (1H, s), 5.14 (1H, t J = 6.6 Hz), 5.43 (1H, t J = 5.8 Hz) and 7.20 - 7.47 (15H, m); ^{13}C NMR (100 MHz) δ 16.56, 18.08, 21.20, 30.64, 35.14, 61.17, 77.04, 86.62, 112.88, 121.81, 126.83, 127.72, 128.67, 137.46, 142.99, 144.32 and 170.27; IR (film) 3055 (m), 3020 (m), 2930 (s), 1740 (s), 1650 (w), 1595 (w), 1490 (m), 1450 (s), 1370 (m), 1240 (s), 1050 (s) and 710 (s) cm^{-1}; MS (m/e); 454 (M^+), 395, 259, 228, 211, 195, 183, 167, 151, 105 (100), 93, 77, 67 and 55. High resolution MS m/e calculated for $C_{31}H_{34}O_3$ 454.24077, found 454.2491.

(2E,6E)-3,7-Dimethyl-1-triphenylmethoxy-2,6-nonadiene (146).

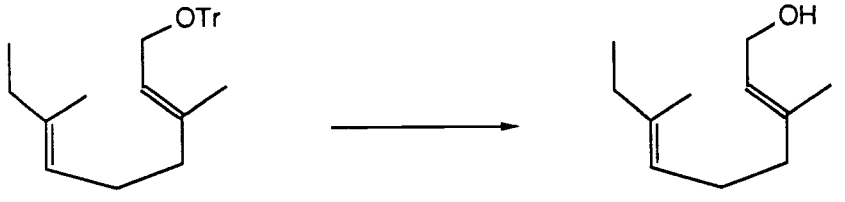


142 146

A dry 1 L, three-necked, round-bottomed flask fitted with a magnetic stir bar, nitrogen inlet and 250 mL addition funnel containing methyl lithium (207 mL, 311 mmol, 1.50 M, Alpha Ventron) was charged with CuI (29.6 g, 155 mmol) and 300 mL of dry ether. The system was purged with dry nitrogen and kept under an inert atmosphere throughout the reaction. After cooling the flask to -20 °C the methyl lithium solution was added dropwise, with vigorous stirring, until the initially formed yellow turbidity clarified to a faint brown

solution. The lithium dimethylcuprate was stirred an additional 5 min. The addition funnel was rinsed with 25 mL of dry ether and charged with 142 (23.5 g, 51.7 mmol) in 100 mL of dry ether. The acetate solution was added dropwise over a 10 min period during which time the reaction went from clear to yellow with a yellow/white precipitate. The reaction was stirred for 1 h at -20 °C and then quenched by the addition of 300 mL of saturated aqueous NH_4Cl. After filtration of the crude reaction mixture through celite, the aqueous layer was drawn off and extracted twice with ether. The combined organic portions were washed repeatedly with 10% ammonia in brine until the blue copper color disappeared. The organic portion was then washed with brine twice, and solvent was removed in vacuo after drying over $MgSO_4$ to yield 21.2 g (100%) of crude 146 as a viscous yellow oil which was not purified prior to use in the subsequent reaction: ^1H NMR (400 MHz) δ 0.99 (3H, t J = 7.5 Hz), 1.47 (3H, s), 1.61 (3H, s), 1.96 -2.13 (6H, m), 3.59 (2H, d J =6.5 Hz), 5.11 (1H, br t J = 6.5 Hz), 5.45 (1H, br t J = 6.5 Hz), and 7.20 - 7.48 (15H, m); ^{13}C NMR (100 MHz) δ 12.79, 15.94, 16.54, 26.25, 32.32, 39.61, 61.28, 86.58, 121.34, 122.47, 126.80, 127.71, 128.69, 137.06, 138.49 and 144.40; IR (film) 3060 (m), 3030 (m), 2960 (s), 2930 (s), 1665 (w), 1600 (w), 1500 (m), 1460 (s), 1390 (w), 1230 (w), 1060 (s) and 715 (s) cm^{-1};

(2E,6E)-3,7-Dimethyl-2,6-nonadien-1-ol (143).

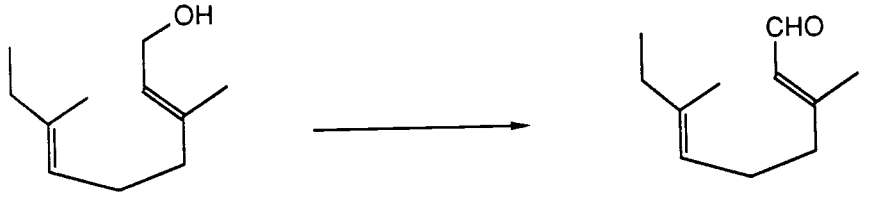


146 143

A 250 mL round-bottom flask containing 144 (21.2 g, 51.7 mmol) and 175 mL of 6% HCl in methanol was stirred at room temperature for 2 h. The reaction was quenched by the addition of K_2CO_3. The reaction mixture was transferred to a separatory funnel and diluted with 300 mL of ether. The organic portion was washed twice with saturated

$NaHCO_3$ followed by brine. The solvent was removed in vacuo, after drying over $MgSO_4$. The crude alcohol was purified by silica gel chromatography (75:25 hexane:ether) to yield 5.2 g (48%) of 143 as a colorless oil: ^1H NMR (400 MHz) δ 0.98 (3H, t J = 7.5 Hz), 1.60 (3H, s), 1.67 (3H, s), 2.01 - 2.14 (6H, m), 4.14 (2H, d J = 6.9 Hz), 5.10 (1H, br t J = 6 Hz) and 5.40 (1H, br t J = 6 Hz); ^{13}C NMR (100 MHz) δ 12.69, 15.78, 16.16, 26.17, 29.61, 32.24, 39.50, 59.18, 122.25, 123.34, 137.14 and 139.44; IR (film) 3320 (br,s), 1670 (w), 1455 (m), 1390 (m) and 1010 (s) cm^{-1}; MS m/e 168 (M^+), 150, 137, 121, 111, 93, 83, 67, 55 (100), 43 and 41.

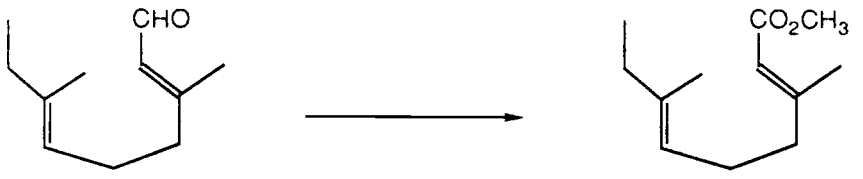
(2E,6E)-3,7-Dimethyl-2,6-nonadienal (147).



143 147

To a 1 L round-bottomed flask containing a stirred suspension of 25 g activated manganese dioxide in 300 mL of hexane at 0 °C was added 143 (5.20 g, 31.0 mmol). The brown suspension was stirred at 0 °C for 30 min. After removal of the manganese dioxide by filtration, it was washed with 300 mL of ether and all solvents were removed in vacuo to yield 4.1 g (80%) of the aldehyde 147. 147 was shown to be >98% pure by glc (column B) and was used without further purification: ^1H NMR (400 MHz) δ 0.97 (3H, t J = 7.5 Hz), 1.26 (3H, s), 1.61 (3H, s), 1.98 (2H, q J = 7.5 Hz), 2.24 (4H, m), 5.07 (1H, br t J = 6.8 Hz), 5.88 (1H, d J = 8.1 Hz) and 10.0 (2H, d J = 8.1 Hz); ^{13}C NMR (100 MHz) δ 12.67, 15.91, 17.56, 25.57, 32.24, 40.62, 120.97, 127.40, 138.43, 163.86 and 191.28; IR (film) 2960 (s, sh), 2930 (s), 2860 (s, sh), 1675 (s), 1635 (m, sh), 1450 (s), 1380 (m), 1200 (s), 1125 (s) and 850 (m) cm^{-1}; MS m/e 166 (M^+), 151, 137, 83, 55 (100) and 41

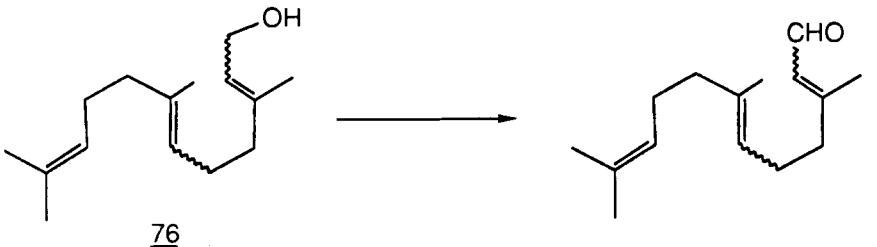
Methyl (2E,6E)-3,7-dimethyl-2,6-nonadienoate (92d).



147 92d

Dry methanol (300 mL) was placed into a 1 L round-bottomed flask and cooled to 0 °C. To this flask was slowly added, with vigorous stirring, 27g of activated manganese dioxide. To this suspension was added 147 (4.10 g, 24.7 mmol) , sodium cyanide (5.00 g, 102 mmol) and 1 mL of glacial acetic acid. The mixture was stirred at room temperature for 24 h at which time 7 mL of saturated sodium bicarbonate was added to neutralize any excess hydrogen cyanide. The manganese dioxide was removed by filtration and washed with 600 mL of ether. The combined organic portions were concentrated in vacuo to an orange slurry. The crude product was extracted from 300 mL of water with ether (3x200 mL), and the combined extracts were washed with water and brine. After drying over $MgSO_4$, the solvent was removed in vacuo to yield, after silica gel chromatography (85:15, hexane ethyl acetate), 1.6 g (33%) of the pure ester as a pale yellow oil. Glc analysis of the product (column B) showed it to be a mixture of the desired (2E,6E) isomer, 92d, (>95%)(with minor contamination by the (2Z,6E) 92b and (2Z,6E) 92c isomers, combined <5%): ^{1}H NMR (400 MHz) δ 0.98 (3H, t J= 7.4 Hz), 1.60 (3H, s), 1.97 (2H, q J = 7.4 Hz), 2.17 (6H, s), 3.69 (3H, s), 5.07 (1H, s, br), and 5.67 (1H, s); ^{13}C NMR (100 MHz) δ 12.72, 15.89, 18.82, 25.89, 32.29, 40.95, 50.75, 115.16, 121.38, 138.05, 160.17 and 167.26;IR (film) 2960 (s), 1720 (s), 1650 (s), 1440 (s), 1230 (s), 1150 (s) and 870 (m) cm^{-1};MS m/e 196 (M^+), 165, 137, 114, 83, 67, 55 (100) and 41;UV (methanol) λ_{max} (n-->π^*) 300 nm ε_{300} = 63, ε_{254} = 1340.

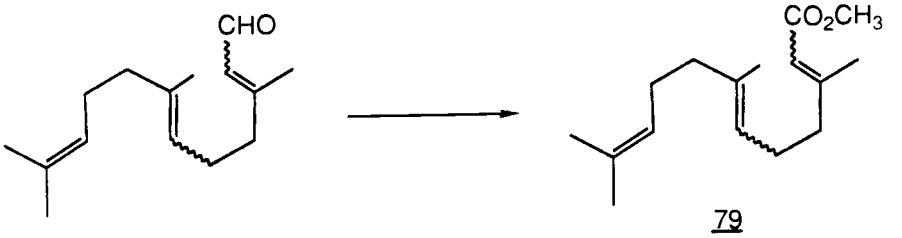
3,7,11-Trimethyl-2,6,10-dodecatrienal (farnesal)



76

A 100 mL round-bottomed flask containing 5 g of activated manganese dioxide, 50 mL of hexane and a magnetic stir bar was cooled to 0 °C. Farnesol, 76a-d, (1.44 g, 6.5 mmol, Fluka, comes as a technical mixture of four E/Z isomers) was added to the flask and the mixture was stirred at 0 °C for 30 min. After removal of the manganese dioxide by filtration it was washed with 150 mL of ether and all solvents were removed in vacuo to yield 1.36 g (95%) of a pale yellow oil which was used without further purification.

Methyl 3,7,11-trimethyl-2,6,10-dodecatrienoate (79) (methyl farnesate)



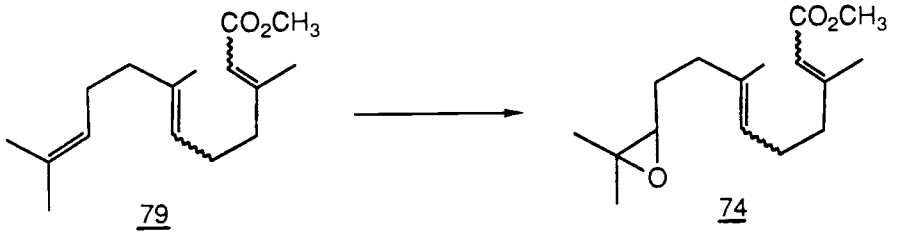
79

Dry methanol (50 mL) was placed into a 100 mL round-bottomed flask and cooled to 0 °C. To this flask was slowly added, with vigorous stirring, 5g of activated manganese dioxide. To this suspension was added farnesal (1.36 g, 6.20 mmol) , sodium cyanide (1.50 g, 3.06 mmol) and 0.5 ml of glacial acetic acid. The mixture was stirred at room temperature for 14 h at which time 2 mL of saturated sodium bicarbonate was added to neutralize any excess hydrogen cyanide. The manganese dioxide was removed by filtration and washed with 150 mL of ether. The combined organic portions were concentrated in vacuo to an orange slurry. The crude product was extracted from 50 mL water with ether (3x50 mL), and the combined extracts were washed with water and

brine. After drying over $MgSO_4$ the solvent was removed in vacuo to give a yellow oil. The crude product was purified by silica gel chromatography (85:15, hexane:ethyl acetate) to yield 1.0 g (65%) of methyl farnesate as a pale yellow oil. Glc analysis of the product (column B) showed it to be a mixture of four E/Z isomers present in a ratio of 1.0 (2Z,6Z):1.5 (2Z,6E):2.4 (2E,6Z):3.0 (2E,6E). 79a, the 2Z,6Z isomer displayed the following spectroscopic properties: ^1H NMR (400 MHz) δ 1.61 (3H, s), 1.68 (7H, s), 1.89 (3H, s), 2.04 (3H, d J = 3 Hz), 2.16 (2H, q J = 7.5 Hz), 2.64 (2H, t J = 7.5 Hz), 3.67 (3H, s), 5.12 (1H, br s), 5.16 (1H, br t J = 7.5 Hz) and 5.66 (1H, s); ^{13}C NMR (100 MHz)(DEPT signals: + = CH_3, CH; - = CH_2; 0 = C) δ 17.60 (+), 23.32 (+), 25.35 (+), 25.68 (+), 26.56 (-), 26.60 (-), 31.88 (-), 33.67 (-), 50.72 (+), 115.77 (+), 124.33 (+), 124.38 (+), 131.49 (0), 135.83 (0), 160.45 (0) and 166.88 (0);IR (solution, CCl_4) 2970 (m), 2936 (m), 1724 (s), 1460 (m), 1434 (m) and 1160 (s) cm^{-1}; MS (m/e) 250 (M^+), 207, 149, 137, 121, 114, 109, 81, 69 (100) and 55: 79b, the 2Z,6E isomer displayed the following spectroscopic properties: ^1H NMR (400 MHz) δ 1.60 (3H, s), 1.62 (3H, s), 1.68 (3H, s), 1.89 (3H, d J = 1.3 Hz), 1.98 (2H, m), 2.05 (2H, m), 2.17 (2H, m), 2.65 (2H, t J = 7.5 Hz), 3.68 (3H, s), 5.09 (1H, br t J ≃ 6.7 Hz), 5.16 (1H, br t J = 7.3 Hz) and 5.66 (1H, s); ^{13}C NMR (100 MHz)(DEPT signals: + = CH_3, CH; - = CH_2; 0 = C) δ 15.93 (+), 17.64 (+), 25.34 (+), 25.66 (+), 26.64 (-), 26.66 (-), 33.40 (-), 39.67 (-), 50.73 (+), 115.74 (+), 123.45 (+), 124.32 (+), 131.30 (0), 135.79 (0), 160.80 (0) and 166.72 (0);IR (solution, CCl_4) 2950 (m), 1722 (s), 1650 (m), 1447 (m) and 1159 (s) cm^{-1}; MS (m/e) 250 (M^+), 207, 149, 137, 121, 114, 109, 81, 69 (100) and 55. 79c, the 2E,6Z isomer displayed the following spectroscopic properties: ^1H NMR (400 MHz) δ 1.60 (3H, s), 1.69 (3H, s), 2.03 (4H, s), 2.16 (7H, sh s), 3.69 (3H, s), 5,09 (1H, br s) and 5.10 (1H, br s); ^{13}C NMR (100 MHz)(DEPT signals: + = CH_3, CH; - = CH_2; 0 = C) δ 17.60 (+), 18.80 (+), 23.32 (+), 25.69 (+), 25.81 (-), 26.48 (-), 31.93 (-), 41.18 (-), 50.76 (+), 115.15 (+), 123.62 (+), 124.12 (+), 131.68 (0), 136.24 (0), 160.11 (0), 167.25 (0);IR (solution, CCl_4) 2950 (m), 1722 (s), 1650 (m), 1447 (m) and 1159 (s) cm^{-1}; MS (m/e) 250 (M^+), 219, 207, 121,

114, 109, 95, 81, 69 (100) and 55. 79d, the 2E,6E isomer displayed the following spectroscopic properties: ^{1}H NMR (400 MHz) δ 1.60 (6H, s), 1.67 (3H, s), 1.98 (2H, m), 2.06 (2H, m), 2.17 (7H, s), 3.68 (3H, s), 5.08 (2H, br s) and 5.67 (1H, s); ^{13}C NMR (100 MHz)(DEPT signals: + = CH_3, CH; - = CH_2; 0 = C) δ 15.91 (+), 17.57 (+), 18.72 (+), 25.57 (+), 25.85 (-), 26.57 (-), 39.58 (-), 40.85 (-), 50.65 (+), 115.15 (+), 122.78 (+), 124.14 (+), 131.28 (0), 136.06 (0), 160.05 (0) and 167.17 (0);IR (film) 2950 (s), 1720 (s), 1650 (s), 1440 (s), 1230 (s), 1150 (s), 1040 (m) and 860 (m) cm^{-1}; MS (m/e) 250 (M^+), 219, 207, 121, 114, 109, 95, 81, 69 (100) and 55.

Methyl 10,11-epoxy-3,7-dimethyl-2,6-dodecdienoate (74a-d).

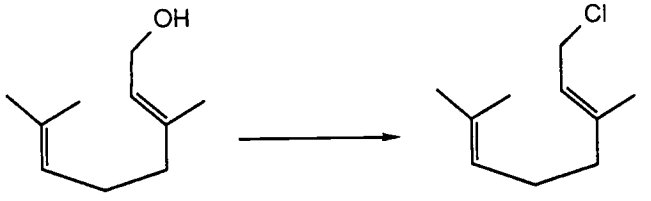


79 74

A 500 mL, three-necked round-bottomed flask fitted with a high speed wire whip stirrer was charged with methyl farnesate, 79, (1.0 g, 4.0 mmol) and 200 mL of water:glyme (1:1.5). The mixture was stirred at high speed and cooled to 0 °C. N-Bromosuccinimide (0.74 g, 4.08 mmol) was added to the flask and the reaction was stirred for an additional 30 min at 0 °C. At this time 100 mL of water was added and the reaction mixture was extracted with ether (3x100 mL). The combined organic portions were washed with brine, dried over $MgSO_4$ and solvent was removed in vacuo to yield the bromohydrin, 135, as a yellow oil which was taken on without further purification. The crude bromohydrin was dissolved in 30 ml of dry methanol and placed in a 50 mL round bottom flask. A magnetic stir bar and K_2CO_3 (1.38 g) were added to the flask. The reaction was stirred at room temperature for 3 h. At this time the crude reaction mixture was poured into 100 mL brine and extracted with ether (3x50 mL). The combined organic portions were washed with brine, dried over $MgSO_4$ and the solvent

removed in vacuo. The crude epoxide was purified by silica gel chromatography (75:25, hexane:ethyl acetate) to yield 0.27 g (26%) of the juvenile hormone, 74a-d, as a pale yellow oil. Glc showed the product to be a mixture of four E/Z isomers whose identity is briefly described in the results and discussion section. MS of the four isomers was obtained; 74a, m/e 266 (M^+), 233, 205, 147, 135, 125, 121, 114, 107, 95, 85, 81, 71, 59, 55, 43 (100) and 41; 74b, m/e 266 (M^+), 233, 205, 147, 135, 125, 121, 114, 107, 95, 85, 81, 71, 59, 55, 43 (100) and 41; 74c, m/e 266 (M^+), 234, 206, 135, 121, 114, 107, 95, 85, 81, 71, 59, 55, 43 (100) and 41; 74d, m/e 266 (M^+), 234, 206, 135, 121, 114, 107, 95, 85, 81, 71, 59, 55, 43 (100) and 41

(2E)-1-Chloro-3,7-dimethyl-2,6-octadiene (132). (geranyl chloride)

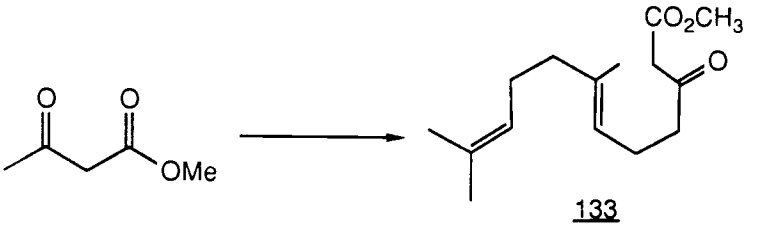


94 132

An oven dried 1 L, three-necked flask fitted with a mechanical stirrer,a nitrogen inlet, a 125 mL addition funnel containing freshly distilled geraniol, 94, (25 g, 162 mmol) dissolved in 50 mL of dry methylene chloride was purged with dry nitrogen and charged with N-chlorosuccinimide (30.0 g, 225 mmol) and 350 mL of dry methylene chloride. After cooling the reaction to 0 °C, 20.0 mL (272 mmol) of dimethylsulfide was added dropwise, via syringe, over a period of 10 min. During the addition the solution turned cloudy. The flask was cooled to -20 °C and the geraniol solution was added dropwise over a 10 min period. After stirring at -20 °C for 10 min the flask was warmed to 0 °C and stirred for an additional 3 h. At this time 500 ml of pentane was added to the flask and the entire contents were poured into 400 mL of cold water. The aqueous layer was drawn off and the organic portion was washed with ice cold brine (2x300 mL). Solvent was removed in vacuo, after drying with $MgSO_4$, yielding 27.8 g (99%) 132 as a dark yellow oil which was used in subsequent reactions without further purification: ^1H NMR (400 MHz) δ 1.60 (3H, s), 1.68

(3H, s), 1.72 (3H, s), 2.08 (4H, m), 4.10 (2H, d J = 8.0 Hz), 5.08 (1H, m) and 5.45 (1H, t J = 8.0 Hz); ^{13}C NMR (100 MHz) δ 16.08, 17.67, 25.64, 26.20, 39.43, 41.13, 120.25, 123.56, 131.94 and 142.75; IR (film) 2970 (s), 2920 (s), 1665 (m), 1450 (s), 1385 (s), 1260 (s), 1115 (w) and 850 (m) cm^{-1}; MS (m/e) 172 (M^+), 136, 129, 123, 81, 69 (100), 68, 67 and 53; BP:75-77 °C (1.8 torr)

Methyl (6E)-7,11-dimethyl-3-oxo-6,10-dodecadienoate (133).

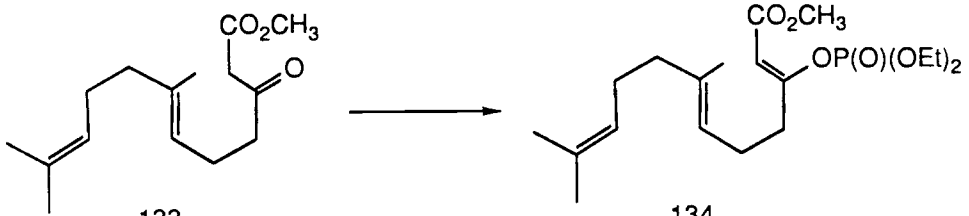


133

A dry 250 mL three-necked flask fitted with a magnetic stir bar and nitrogen inlet was charged with sodium hydride (0.695 g, 28.9 mmol in a 60% dispersion of mineral oil). This was washed with two 50 mL portions of dry pentane before 50 mL of dry THF was added and the flask cooled to 0 °C. Methyl acetoacetate (2.84 mL, 3.05 g, 26 mmol) was added dropwise, via syringe, to the sodium hydride suspension over a period of 20 min resulting in a pale yellow solution. To this solution of the monoanion was added n-butyllithium (17.0 mL, 1.55 M, Aldrich), via syringe, over a 10 min period. The resulting orange solution was stirred an additional 20 min at 0 ° before 132 (5.00 g, 28.9 mmol) was added dropwise, via syringe, over a period of 5 min. The solution was warmed to room temperature and stirred an additional 30 min. The reaction was quenched by the cautious addition of 21 mL of HCl (3 M). The reaction mixture was diluted with 75 ml of ether and after separation the aqueous phase was extracted with ether (3x50 mL). The combined organic portions were washed with water (3x50 mL) and dried over $MgSO_4$ prior to removal of solvent in vacuo. The crude product, 133, was used in subsequent reactions without further purification. However, for characterization 133 could be purified by either silica gel chromatography (90:10, hexane:ether) or distillation at reduced pressure (< 1 torr): ^{1}H NMR (400 MHz) δ 1.60 (3H, s),

1.61 (3H, s), 1.68 (3H, s), 1.97 (2H, m), 2.07 (2H, m), 2.29 (2H, m), 2.57 (2H, t J = 7.5 Hz), 3.45 (2H, s), 3.74 (3H, s) and 5.07 (2H, m); ^{13}C NMR (100 MHz) δ 15.95, 17.63, 22.11, 25.64, 26.55, 39.59, 43.04, 49.07, 52.28, 121.98, 124.10, 131.43, 136.77, 167.61 and 202.44; IR (film) 2920 (s), 2860 (s); 1740 (s), 1720 (s), 1660 (m), 1635 (m), 1450 (s) and 1050 (m) cm^{-1}; MS (m/e) 252 (M^+), 209, 136, 109, 105, 101, 81 and 69 (100).

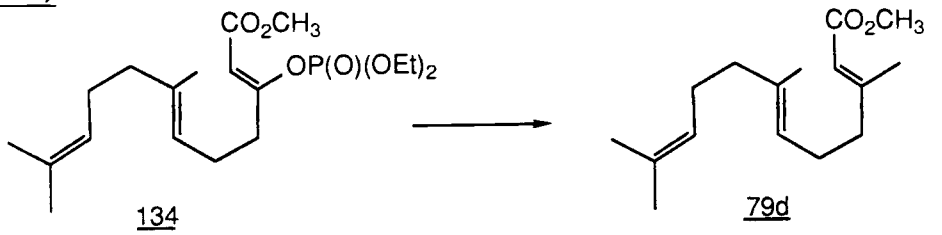
Methyl (2E,6E)-3-(diethoxyphosphoryloxy)-7,11-dimethyl-2,6,10-dodecatrienoate (134).



133 134

A dry 100 mL round-bottomed flask, fitted with a magnetic stir bar and nitrogen purge was charged with sodium hydride (0.105 g, 4.40 mmol in a 60% dispersion of mineral oil) . This was rinsed twice with dry pentane prior to addition of 50 mL of dry THF. The flask was cooled to 0 °C and 133 (1.00 g, 3.97 mmol) in 3 mL of THF was added dropwise, via syringe, over 5 min. The solution was stirred an additional 10 min at 0 °C prior to addition of diethylchlorophosphate (0.719 g, 4.17 mmol) in 3 mL of THF, dropwise. The mixture was then stirred at 0 °C for 30 minutes at which time the reaction was quenched by the addition of 50 ml of water. An additional 50 mL of ether were added to the reaction and after separation the combined organic portions were washed with brine (2x50 mL). After drying the organic layer with $MgSO_4$, solvent was removed in vacuo leaving 1.59 g (93%) of 134 as an orange oil. This material was taken on in the synthetic scheme without further purification.

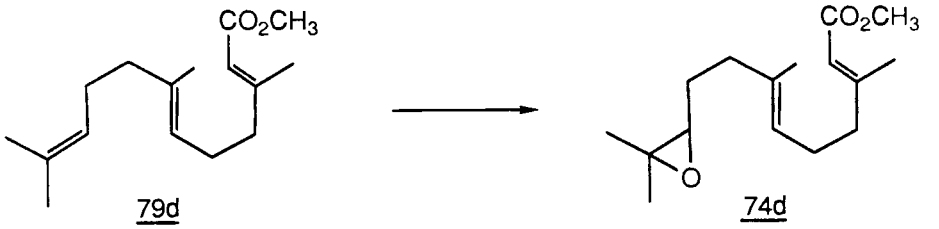
Methyl (2E,6E)-3,7,11-trimethyl-2,6,10- dodecatrienoate (79d) (methyl farnesate).



134 79d

A dry 50 mL round-bottomed flask, fitted with a magnetic stir bar and nitrogen purge, was charged with cuprous iodide (0.733 g, 3.80 mmol) and 20 mL of dry ether. The stirred suspension was cooled to 0 °C and methyllithium (5.70 mL, 7.63 mmol, 1.35 M, Alpha Ventron) was added to yield a clear, light brown solution of lithium dimethylcuprate. The solution was stirred at 0 °C for 5 min then cooled to -78 °C and stirred for an additional 15 min. At this time 134 (0.746 g, 1.92 mmol) in 3 mL of dry ether was slowly added to the cuprate solution and stirred for 2 h at -78 °C followed by warming to -47 °C (cyclohexanone/dry ice bath) for 1 h. The reaction was quenched with saturated NH_4Cl and diluted with 50 mL of ether. The aqueous layer was separated and extracted twice with ether. The combined organic portions were washed repeatedly with 10% ammonia in brine until the blue copper color disappeared followed by one wash with brine and drying over $MgSO_4$. After removal of the solvent in vacuo the oily residue was distilled at reduced pressure (1 torr) in a kugelrohr (Aldrich). The crude ester was purified by silica gel chromatography (75:25, hexane:ethyl acetate) to yield 0.256 g (53%) of 79d as a colorless oil: ^1H NMR (400 MHz) δ 1.60 (6H, s), 1.67 (3H, s), 1.98 (2H, m), 2.06 (2H, m), 2.17 (7H, s), 3.68 (3H, s), 5.08 (2H, br s) and 5.67 (1H, s); ^{13}C NMR (100 MHz)(DEPT signals: + = CH_3, CH; - = CH_2; 0 = C) δ 15.91 (+), 17.57 (+), 18.72 (+), 25.57 (+), 25.85 (-), 26.57 (-), 39.58 (-), 40.85 (-), 50.65 (+), 115.15 (+), 122.78 (+), 124.14 (+), 131.28 (0), 136.06 (0), 160.05 (0) and 167.17 (0); IR (film) 2950 (s), 1720 (s), 1650 (s), 1440 (s), 1230 (s), 1150 (s), 1040 (m) and 860 (m) cm^{-1}; MS (m/e) 250 (M^+), 219, 207, 121, 114, 109, 95, 81, 69 (100) and 55.

Methyl (2E,6E)-10,11-epoxy-3,7-dimethyl-2,6-dodecadienoate (74d).



79d 74d

The procedure used is identical to that used for the mixture of four E/Z isomers described previously. A 500 mL, three-necked round-bottomed flask fitted with a high speed wire whip stirrer was charged with methyl farnesate, 79d, (1.0 g, 4.0 mmol) and 200 mL of water:glyme (1:1.5). The mixture was stirred at high speed and cooled to 0 °C. N-Bromosuccinimide (0.74 g, 4.08 mmol) was added to the flask and the reaction was stirred for an additional 30 min at 0 °C. At this time 100 mL of water was added to the reaction and extracted with ether (3x100 mL). The combined organic portions were washed with brine, dried over $MgSO_4$ and solvent was removed in vacuo to yield the bromohydrin, 135, as a yellow oil which was taken on without further purification. The crude bromohydrin was dissolved in 30 mL of dry methanol and placed in a 50 mL round-bottomed flask. A magnetic stir bar and K_2CO_3 (1.38 g) were added to the flask. The reaction was stirred at room temperature for 3 h. At this time the crude reaction mixture was poured into 100 mL brine and extracted with ether (3x50 mL). The combined organic portions were washed with brine, dried over $MgSO_4$ and the solvent removed in vacuo. The crude product was purified by silica gel chromatography (75:25, hexane:ethyl acetate) to yield 0.2434 g (23%) of the juvenile hormone, 74d, as a pale yellow oil: ^{1}H NMR (400 MHz) δ 1.26 (3H, s), 1.30 (3H, s), 1.63 (5H, br s), 2.05-2.26 (9H, m with 6H, d J = 3.4 Hz buried), 2.70 (1H, t J = 6.3 Hz), 3.68 (3H, s), 5.14 (1H, br s) and 5.67 (1H, s); ^{13}C NMR (100 MHz) δ 15.99, 18.70, 18.77, 24.83, 25.87, 27.40, 36.27, 40.78, 50.75, 58.26, 64.05, 115.27, 123.45, 135.29, 159.88 and 167.19; IR (film) 2950 (s), 1720 (s), 1650 (s), 1430 (br,s), 1220 (s), 1150 (s) and 870 (m) cm^{-1};, MS m/e 266 (M^+), 234, 206, 135, 121, 114, 107, 95, 85, 81, 71, 59, 55, 43 (100) and 41; UV (methanol) ε_{254} = 1200

B.PHOTOLYSES

Photolysis of methyl geranate in ether. A solution of methyl geranate (0.182 g, 1 mmol) and dodecane (0.017 g, 0.1 mmol) in 10 mL of dry ether was degassed and irradiated for 8 hours at 253.7 nm. Ether was removed in vacuo and the crude mixture was analysed by glc (column A). The gas chromatogram revealed five new product peaks, which were separated and collected by preparative glc (column E), as well as starting material. The identity of each peak (in order of increasing retention time) was found to be: 98 (4.2%), ^{1}H NMR (400 MHz) δ 1.60 (3H, s), 1.65 (3H, s), 1.72 (3H, s), 2.24 (1H, p J = 7.3 Hz), 2.48 (1H, p J = 7.3 Hz), 3.01 (1H, t J = 7.6 Hz), 4.86 (1H, s), 4.87 (1H, m) and 4.99 (1H, tt J = 7.0, 1.0 Hz); ^{13}C NMR (100 MHz) δ 17.79, 20.39, 25.74, 28.93, 51.78, 53.20, 113.64, 121.05, 131.53, 142.39 and 173.95; IR (film) 2920 (m), 1730 (s), 1650 (w) and 1160 (m) cm^{-1}; MS (m/e) 182 (M^{+}), 139, 123, 122, 114, 107, 83, 82, 81, 69 (100) and 53; UV (methanol) end absorbance. 72 (5.9%), ^{1}H NMR (400 MHz) δ 0.75 (3H, s), 1.10 (3H, s), 1.11 (3H, s), 1.45, (1H, m), 1.55 (1H, m), 1.69 (1H, m), 2.30 (1H, s), 2.74 (1H, s) and 3.66 (3H, s); ^{13}C NMR (100 MHz) δ 13.03, 16.97, 18.58, 23.62, 29.23, 43.18, 46.89, 50.09, 50.84, 53.25 and 173.78; IR (film) 2950 (s), 1730 (s), 1450 (s), 1440 (s), 1380 (s), 1050 (s) and 900 (m) cm^{-1}; MS (m/e) 182 (M^{+}), 123 (100), 122, 107, 81, 79, 67 and 55; UV (methanol) end absorbance . 73 (6.8%), ^{1}H NMR (400 MHz) δ 0.91 (3H, d J = 7 Hz), 1.35-1.53 (2H, m), 1.71 (3H, s), 1.85-2.00 (2H, m), 2.41 (1H, br q J = 7 Hz), 2.78 (1H, t J = 9.2 Hz), 2.99 (1H, br q J = 8.4 Hz), 3.67 (3H, s), 4.70 (1H, br s) and 4.72 (1H, br s); ^{13}C NMR (100 MHz) δ 16.90, 20.75, 30.58, 34.07, 36.94, 48.49, 51.19, 52.04, 109.37, 146.93 and 174.98; IR (film) 3050 (m), 2980 (s), 2875 (m,sh), 1730 (s), 1650 (s), 1440 (br, s), 1380 (br,s), 1170 (br, s) and 890 (s) cm^{-1}; MS (m/e) 182 (M^{+}), 167, 151, 139, 123, 114, 107, 83, 81, 69 (100) and 55. UV (methanol) end absorbance. 100 (5.7%), ^{1}H NMR (400 MHz) δ 1.62 (3H, s), 1.69 (3H, s), 1.77 (3H, s), 2.71 (2H, t J = 7.2 Hz), 3.08 (2H, s), 3.68 (3H, s), 5.08 (1H, br t J = 7.2 Hz) and 5.33 (1H, br t J = 7.2 Hz);^{13}C NMR

(100 MHz) δ 71.67, 23.91, 25.66, 27.23, 37.33, 51.78, 122.33, 127.78, 127.82, 132.00 and 171.96; IR (film) 2975 (s), 2918 (s), 2858 (s, sh), 1735 (s), 1436 (s), 1302 (m), 1259 (s) and 950 (m) cm^{-1}; MS (m/e). 97 (41.6%), ^1H NMR (80 MHz) δ 1.61 (3H, s), 1.67 (3H, s), 1.87 (3H, d J = 1.5 Hz), 2.16 (2H, m), 2.62 (2H, m), 3.67 (3H, s), 5.12 (1H, br t J = 7.2 Hz) and 5.63 (1H, s); ^{13}C NMR (20 MHz) δ 17.39, 25.08, 25.50, 26.87, 33.44, 50.33, 115.91, 123.82, 131.82, 160.06 and 166.29; IR (film) 2970 (br,s), 1720 (s), 1650 (m), 1430 (m), 1220 (s), 1140 (s) and 1050 (w) cm^{-1}; MS (m/e) 182 (M^+), 123, 83, 82, 69 (100) and 53; UV (methanol) λ_{max} 218 nm (π -> π*), ε = ??? and 300 nm (n -> π*), ε = ??? (RERUN!!!!!!!), absorbance at 254 nm = ????.

Photolysis of methyl geranate with 1,2-dimethylimidazole. A solution of methyl geranate, 71, (0.182 g, 1 mmol) and 1,2-dimethylimidazole (0.024 g, 0.24 mmol) in 10 mL of dry ether was degassed and irradiated for 5 hours with 254 nm light. At this time the photolysis mixture was washed with 5% HCl, saturated $NaHCO_3$ and brine. The ether was removed, after drying with $MgSO_4$, in vacuo and the reaction mixture analysed by glc (column A). In addition to products 98, 72, 73, 100, 97 and starting material 71, two new products were isolated by preparative glc (column D) and characterized spectroscopically . 99: ^1H NMR (400 MHz) δ 1.61 (3H, s), 1.69 (3H, s), 2.12 (4H, s), 3.06 (2H, s), 3.68 (3H, s), 4.91 (1H, s), 4.95 (1H, s) and 5.10 (1H, br s);^{13}C NMR (20 MHz) δ 17.69, 25.69, 26.27, 36.01, 41.93, 51.67, 113.69, 123.87, 131.85, 142.43 and 171.81; IR (film) 2900 (s), 1740 (s), 1650 (w), 1440 (m), 1160 (m), 1020 (m) and 900 (m) cm^{-1}; MS (m/e) 182 (M^+), 122, 109 (100), 107, 95, 83, 81, 73, 67, 59, 55 and 53; UV (methanol) end absorbance. 101, ^1H NMR (400 MHz) δ 1.63 (3H, s), 1.69 (3H, d J = 1 Hz), 1.71 (3H, s), 2.73 (2H, t J = 7.5 Hz), 3.00 (2H, s), 3.68 (3H, s), 5.10 (1H, t J = 7.5 Hz) and 5.25 (1H, t J = 7.5 Hz); ^{13}C NMR (100 MHz) δ 16.20, 17.69, 25.64, 27.17, 44.79, 51.67, 122.41, 128.00, 128.21, 131.95 and 172.48;IR (film) 2975 (s), 2918 (s), 2858 (s, sh), 1735 (s), 1436 (s), 1302 (m), 1259 (s) and 950 (m) cm^{-1}; MS (m/e) 182 (M^+), 135, 124 (100), 123, 111, 109, 107,

95, 91, 81, 79, 72, 67, 55 and 53; UV (methanol) end absorbance.

Photolysis of methyl geranate and propiophenone in benzene.

A solution of methyl geranate, 71, (0.100 g, 0.55 mmol) and propiophenone (0.4 g, 3 mmol) in 10 mL of dry benzene was irradiated for 20 hours with 254 nm light. After removal of benzene in vacuo the mixture was analysed by glc (column A) and was found to consist of 72 (19%), 73 (22.6%), 97 (26.6%)and starting material, 71 (26.7%).

Photolysis of methyl geranate, (71), in ether, time vs composition.

A solution of methyl geranate (0.455 g, 2.5 mmol) and dodecane (42 mg, 0.25 mmol) in 25 ml of ether was divided among 20 quartz photolysis tubes. After degassing, two tubes were wrapped in aluminum foil and all were placed into the Rayonet reactor and irradiated with 254 nm light. Two tubes were removed at each of the following time intervals: 0.5, 1, 2, 4, 8, 12, 18.5, 30 and 48 h. The tubes wrapped in aluminum foil were in the reactor for the entire 48 h. All samples were analysed by glc (column B). Analysis results are presented in the discussion and results section (Figure 12).

Photolysis of Methyl (2E,6E)-3,7-dimethyl-2,6-nonadienoate (92d) in ether, time vs comoposition.

A solution of 92d (0.196 g, 0.001 mol)and dodecane (0.019 g, 1.1 x 10^{-4} mol) in 10 mL of ether was divided among 10 quartz photolysis tubes. After degassing in the usual way, the tubes were placed into the Rayonet reactor and irradiated with 254 nm light. two tubes were removed at each of the following time interval: 1.3, 2, 4, 8 and 12 Hr. Samples were analysed by glc (column B). Analysis results are presented in the discussion and results section (Figure 25).

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